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Review

Significance of Genetic and Biochemical Mediators in Delineating the Clinical Manifestation of Asthma

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Abstract

"The Global Impact of Respiratory Disease" forum considers asthma as one of the paramount respiratory diseases in the world. This common chronic disease affects the quality of life in all age group people and may cause premature death. Asthma is an inflammatory disease identified, with intermittent cough, wheeze, and shortness of breath brought by characteristic triggers and relieved by bronchodilating medications. Varied definitions to this complex disorder are befitting as it may include progressive lung impairment and in some patients, eventuate in partially reversible or irreversible airway obstruction. Epithelial cells and smooth muscle cells are the two airway cell types crucial in asthma pathogenesis. The regulation and activation of cytokines and chemokines and the scheme of airway injury may provide insights into novel therapeutic targets. The prime role of IgE in pathogenesis has led to the focus towards humanized monoclonal antibodies as a possible treatment. It is reported that an initial small set of genes activate the risk in susceptible individuals which in turn are modulated by another set of genes along with environmental cues. Identification of specific genes and variation within those, which leads to this menace, has been an ultimatum in asthma research. This syndrome collectively highlights on the importance of family history, overlapping phenotypes with specific clinical, physiological characteristics, genetic, environmental risk factors, and their interactions. The root causal inflammatory signals with noticeable biomarkers, co morbidities and response to therapies are less explored. The cornerstone of asthma pathogenesis and its treatment is about inflammation control; remodel the air flow and their ensuing symptoms. On a regular basis, certain preventive medications can treat inflammation of the airways, hence can reduce flare-ups. Hence they are used to keep asthma under control. Effective management depends on promoting patients to adhere to treatment and clinicians to guidelines.

Keywords: Asthma, hypersensitivity, immunoglobulins, exacerbations, cytokines, asthma care.

Introduction

Asthma and allergy are common conditions with heterogeneous etiologies. Allergy refers to a deleterious immune-mediated inflammatory response to otherwise normally harmless substances known as allergens, resulting in one or more diseases such as asthma, allergic rhinitis, atopic dermatitis and food allergy. Antibodies, white blood cells, mast cells, complement proteins and other substances (part of humoral and cellular defense), protects the body against foreign substances which are called antigens. In susceptible people, the immune system can inflate when exposed to certain allergens present in the environment, foods or drugs which results in an allergic reaction. On first exposure to an allergen, the immune system produces specific antibody called immunoglobulin E-IgE. If IgE is not involved, these reactions are called hypersensitivities.

Atopy which refers to the ability to synthesize excessive IgE antibodies to environmental allergens remains a major threat in asthma pathogenesis (NAEAP, 2002). IgE binds to cells called basophils in the bloodstream and to mast cells (identical to basophils) in the tissues. On first exposure, these allergens does not cause symptoms, rather sensitizes people, but on the second encounter with the allergens, in the sensitized people, the basophils and mast cells with IgE on their surface release substances that cause inflammation in the vicinity. These substances initiate a gush of reactions that irritates and harm tissues continuously and causes hypersensitivity in some individuals and not in others which still is considered as a puzzling phenomenon. Epidemiology studies have shown that asthma is a complicated disease influenced by genetic and environmental factors (Gilmour, 2000; Tizaoui *et al.*, 2017).

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Allergens may acquire certain unique structural or bioactive properties (Lehrer *et al.,* 1996), which contributes to airway hyperactivity. Asthma, a form of anaphylactic reaction is a combination of edema of throat lining and airways and airway constriction averting tissues from getting sufficient oxygen, leading to breathing interference. Asthma sometimes could be fatal resulting in a rapid fall of blood pressure due to dilation of blood vessels causing exacerbations, a kind of attack. This disease is diversified in regard to natural history of the people, their immunopathology, clinical phenotypes, and response to therapies (Holgate, 2008). In India, based on previous reports, the prevalence rate of asthma ranges from 2% to as high as 23%. Such marked variation is due to wide geographical and environmental disparity in India. Most patients in India still consider asthma a stigma; hence try to conceal the disease. Many assume that inhalers are habit forming and strong. Many patients abide to treatment when they cannot bear their symptoms and stop when symptoms subside. Despite these setbacks, with frequent and regular patient education programmes, the acceptability of inhaler treatment for asthma is gradually improving (Singh, 2018; Marks *et al.,* 2018; GINA, 2019). Since this subject is of expansive nature, this review will attempt to provide an overview of the clinical manifestations, immunologic events that occur in IgE-mediated hypersensitivity reactions, gene associations, patient education, prevention and management aspects of asthma.

Course of asthma

Etiology: Asthma has conventionally been classified as either allergic- or non-allergic. Typically, each patient has a unique list of triggering factors causing increased symptoms or "flares". Plethora of ordinary substances that trigger allergic reactions are shown in Table 1 (Wardlaw, 1993; Camargo *et al.,* 1999). Others include gastroesophageal reflux disease, obesity and genetic factors. Individual's susceptibility is also controlled by other biological factors such as stress (emotional well-being), pre-existing disease etiology and a number of viable interactions among antigens, antigen-presenting and immune cells, inflammatory cells and soluble mediators (Husband and Gleeson, 1996; Gilmour, 2000).

Multiple risk factors associated with asthma

1. Family history of asthma in parents or siblings
2. Abnormal lung function in younger age
3. Viral infections in childhood

In utero exposure in smoking mothers during pregnancy (CDC 2011, GINA 2019).

Asthma with episodic symptomatology has been recognized since many decades. Symptoms of asthma include the following:

Table 1. Triggering factors that increases the asthmatic symptoms.

Airborne allergens	Pollens, molds, household dust including dust mite and cockroach antigens, animal dander, other air pollutants (e.g., ozone [03], sulfates, nitrogen oxides, and particulate matter)
Exercise	No or less stretching of the airways or hyperventilation
Atopic diseases	Chronic sinusitis (persistence of asthma from child into adult)
Drug induced hypersensitivity	Non-Steroidal Anti-Inflammatory drugs (NSAIDs) and beta-adrenergic receptor blockers
Irritants	Household sprays, paint fumes, detergent enzymes, industrial chemicals, tobacco smoke
Occupational settings	Latex, gums, wood dust and fluxes
Antibiotics	Babies treated with antibiotics may be 50% more likely to develop asthma
Physiological and psychological	Anaemia and depression in mother can be co- related to asthmatic stress in the child

1. Difficulty in breathing
2. Wheezing, a whistling sound in the chest
3. Dry cough
4. Shortness of breath
5. Chest tightness
6. Common cold (runny or stuffy nose)
7. Tachycardia
8. Dyspnea
9. Sleep issues
10. Mood irritations

Unfortunately in some cases, symptoms can lead to permanent lung damage. These symptoms often get worse when people are exposed to any of the triggering factors (Morris, 2019) as mentioned in Table 1.

Variables that determine asthma classification

Based on severity of illness prior to therapy, frequency of day and night symptoms and lung function, asthma is classified. Frequency of exacerbations, rescue inhaler use and assessment of the disorder's effect on normal activity also play a major role (NIH, 2011; Chung *et al.,* 2014; GINA, 2019) (Table 2).

Classification based on clinical symptoms: Few other diagnostic tools also assess lung efficiency. FEV1, Forced Expiratory Volume in one second evaluates the exhalation ability of lungs (Pulmonary function test) and PEF is Peak Expiratory Flow.

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Table 2. Classification of asthma and its treatment.

Classification	Intermittent asthma	Mild persistent asthma	Moderate persistent asthma	Severe persistent asthma
Symptoms	• wheezing or whistling when breathing • coughing • swollen airways • development of mucus in the airways	• wheezing or whistling when breathing • coughing • swollen airways • development of mucus in the airways • chest tightness or pain	same as mild persistent asthma	same as mild persistent asthma
Treatment	-rescue inhaler -daily medication not required	-low-dose inhaled corticosteroid medication, usually taken daily. - rescue inhaler required if symptoms occur time to time.	-slightly higher dose of inhaled corticosteroid that's used for mild persistent asthma -rescue inhaler also required	-limit physical activities -inhaled corticosteroids at a higher dose than with other asthma types -oral corticosteroids at a higher dose than with other asthma types -rescue inhaler -medications that will help combat the trigger

Intermittent asthma:
Symptoms are mild.
1. Up to two days per week or two nights per month.
2. Will usually not hinder any of your activities and can include exercise-induced asthma.
3. FEV1 or PEF ≥ 80%.
4. Pulse rate per minute < 100.

Most people with asthma have mild symptoms. Mild intermittent and mild persistent are the most common types of asthma. Mild asthma is more likely to be untreated than other types since the symptoms are so mild.

Mild persistent asthma:
Symptoms are still mild
1. Occur more than twice per week; don't have symptoms more than once per day.
2. FEV1 or PEF ≥ 80%.
3. Pulse rate per minute < 100.

Moderate persistent asthma:
1. Symptoms once each day, or most days. May occur one night each week (exacerbations may affect activity and sleep)
2. FEV1 or PEF 60-80%.
3. Pulse rate per minute 100-120.

Severe persistent asthma:
1. Symptoms several times during the day, many nights each week. It doesn't respond well to medications even when taken regularly.
2. FEV1 or PEF ≤ 60%.
3. Pulse rate per minute > 120.

Sputum of asthmatics: The inflammation of asthma is elucidated by eosinophilia and metachromatic cells in sputum and it helps in perceiving the cellular characteristics of airway inflammation (Gibson *et al.*, 1989). In the sputum of such patients, microscopic spiral-shaped mucus plugs called Curschmann's spirals from subepithelial mucous gland ducts of bronchi crop up. They are desquamated epithelium appearing in their lavages, seen in association with creola bodies and Charcot-Leyden crsytals, which are elongated microscopic mucous casts from small bronchi (Curschmann's spiral-archives, 2009).

Diagnosis

A physical examination of nose, throat and upper airways is conducted. Monitoring breath using stethoscope may show wheezing (high-pitched whistling sounds) which may mean asthma, but physically may look normal. As mentioned in Table 3, several other tests are performed (Pruitt, 2018). In acute asthma patients, pulse oximetry measurement is desirable to exclude hypoxemia.

Radiography: In most individual with symptoms of asthma, chest radiograph remains the initial imaging evaluation tool (NAEPP, 2007). It reveals hyperinflation and increased bronchial markings with evidence of atelectasis, a parenchymal disease with complete or partial inflation of the lung, pneumonia, congenital anomaly, or a foreign body.

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Table 3. Non-invasive diagnostic evaluations in determining the severity of asthma.

Breathing Test	Pulmonary function tests	Exercise test	Fraction of exhaled nitric oxide test	Allergy test
Recorded before and after inhaling dry mixture of gases to see if breathing function is worse- known as a eucapnic voluntary hyperventilation test.	Spirometry (peak flow meter) and plethysmography (to measure lung function and capacity)	Breathing test can be observed before exercise to see if breathing function is worse (bronchoconstriction) or after exercise (with monitoring of the electrocardiogram and oxyhemoglobin saturation)	Non-invasive marker of airway inflammation	Can identify allergic factors that may significantly contribute to asthma (such as eczema and hives)

Table 4. Involvement of multiple cell types and their molecules in pathobiology of asthma.

Cell type	Molecules	Role in asthma pathobiology
Eosinophils	IL-12, *IFNγ*	TH-1 response
	IL-4, 5, 13	TH-2 response
	IL-10	Inhibition of immune response
	Leukotrienes	Inflammation
	TGF-β	Fibrosis and remodelling
Neutrophils	IL-8, GM-CSF, G-CSF	Increase and spread of inflammatory cells
	TNFα, , IL-1	Inflammation
	TGF-β, VEGF	Airway remodelling
	Proteases, oxygen free radicals	Tissue damage
Mast cells	TNFα, TGF-β, FGF, tryptase, chymase	Airway remodelling
Macrophages	IL-8, GM-CSF, TNFα, MIP-1	Increase and spread of inflammatory cells
	IL-12, *IFNγ*	TH-1 response
	IL-10	Inhibition of immune response
	Prostaglandins	Inflammation
Lymphocytes	IL-4, 5, 13	TH2 response
	IFNγ	TH1 response
	IgE	Allergic response
Epithelial cells	IL-8, MCP-1	Increase and spread of inflammatory cells
	IL-4, 5, 13	TH-2 response
	IL-10,	Inhibition of immune response
	TGF-β	Fibrosis and remodelling
	EGFR	Airway remodeling

IL-Interleukin, IFNγ-Interferon- gamma, GM-CSF/G-CSF-Granulocyte Monocyte / Granulocyte Colony Stimulating factor, TNFα-Tumor Necrosis Factor alpha, TGF β-Transforming Growth Factor beta, VEGF-Vascular Endothelial Growth Factor, MCP-1-Monocyte Chemotactic protein-1,EGFR-Epidermal Growth Factor Receptor, FGF-Fibroblast Growth Factor, MIP-Macrophage Inflammatory Protein, IgE-Immunoglobulin E.

Histologic evaluation of the airways: Typically reveal infiltration with inflammatory cells, narrowing of airway lumina, bronchial and bronchiolar epithelial denudation and fibrosis, myocyte hyperplasia, neovascularisation and mucus plugs (Thomson *et al.,* 2004). Figure 1 represents histology of asthmatic airway in tissue section of lung showing inflammation and remodeling (Elias *et al.,* 2003).

Differential diagnosis: Sometimes diagnosis and management can be herculean as few diseases can mimic asthma (NIH, 2011; NICE, 2019).

- Chronic Obstructive Pulmonary Disease (e.g., chronic bronchitis or emphysema)
- Congestive heart failure
- Pulmonary embolism
- Mechanical obstruction of the airways (benign and malignant tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (e.g., angiotensin-converting enzyme inhibitors)
- Vocal cord dysfunction

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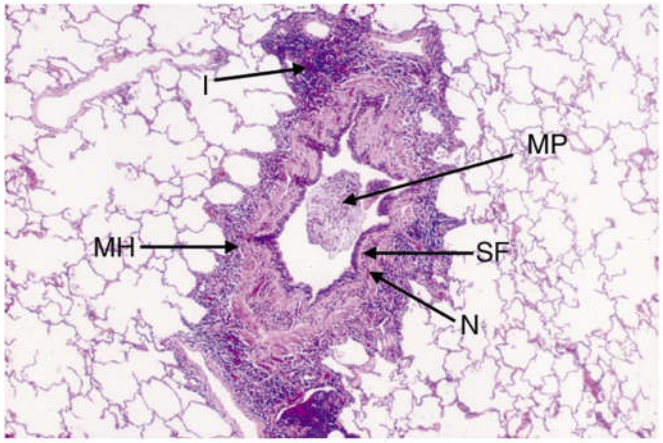
Figure 1. Inflammation and remodeling in the asthmatic airway of lung section. There is impressive inflammation (I), mucus plugging (MP), Subepithelial Fibrosis (SF), Myocyte Hypertrophy and Hyperplasia (MH), and Neovascularization (N) in the section.



Source: Elias *et al.* (2003).

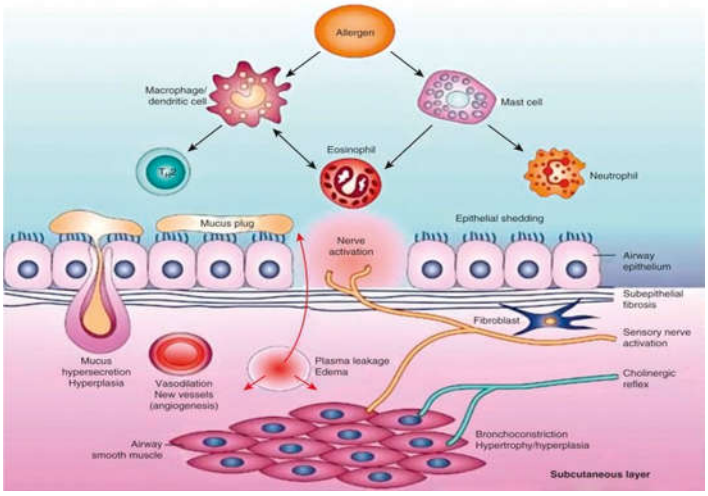
Pathophysiology of asthma: Pathogenesis of asthma is complex and involves airways distinguished by airway hyper-responsiveness, eosinophilic infiltration, reversible airflow obstruction, airway remodeling, mucus hypersecretion, and goblet cell hyperplasia (Bousquet *et al.,* 2000; Kay, 2005). In this airway disorder, many cell types like mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells play a role (Table 4) (Bethesda, 2007; Finiasz *et al.,* 2011).

Inflammation and Asthma: Bronchial reactions show changes, which are dependent upon the disease's severity, treatment, and duration. Infiltration of the airway by inflammatory cells such as activated lymphocytes and eosinophils, epithelial denudation, deposition of collagen in the sub-basement membrane area and mast cell degranulation are often, but not always, the features of mild persistent asthma. Epithelial damage and shedding followed by the release of broncho-constrictor neuropeptides, diminished production of epithelial cell-derived relaxant factors, synthesis of pro-inflammatory mediators and endothelin from the epithelium itself is eventuated by the exposure of intraepithelial nerves, which may be due to heightened bronchial responsiveness (Vanhoutle, 1988, Springall *et al.,* 1991). Hence disintegration in the permeability barrier, loss of equilibirium and disruption of mucociliary molecules (Montefort *et al.,* 1992) occurs**.** In severe asthma, a cascade of events like bronchial lumen occlusion by mucus, hypertrophy of the bronchial smooth muscle and goblet cell hyperplasia is observed (kraft *et al.,* 1999). The cellular profile of inflammation in asthma, highlights the following:

1. Nature of the immune reaction of injury
2. Potential mechanisms by which such responses occur, resulting alteration in physiology and
3. Possible therapeutic targets necessary to regulate, reverse, or prevent such events.

IgE antibodies have been linked to the severity of asthma and the airway's early response to allergens. In brief, IgE binds to mast cells and basophils and release mediators like histamine and cysteinyl leukotrienes such as C 4. The cohort of these pro-inflammatory proteins suggests that mast cells can aid to both acute and chronic inflammation. Granular proteins from mature eosinophil released as inflammatory mediators and eosinophilic infiltration persay in mucosal airway tissue is also found in many patients with chronic, persistent asthma. All these sequential events could injure airway epithelium, enhance bronchial responsiveness, and affect the regulation of acetylcholine and its subsequent release leading to smooth muscle contraction (Montefort *et al.,* 1992). Figure 2 shows the cascade of reactions in airways subsequent to an allergen attack (Barnes, 2004).

Fig. 2. Pathobiology of asthma. Allergen driven cascade of reaction in lung airways.



Source: Barnes (2004).

T-helper 1 and T-helper 2 (Thl andTh2)–A disparity: Airway inflammation may represent a loss of normal balance between two "opposing" populations' of T lymphocytes viz., Th 1 and Th2. Th-1 cells are pivotal in cellular defense mechanisms in response to infection whereas Th2 can arbitrate allergic inflammation. So Th2-type T cells may play a role in the pathogenesis of mild to moderate asthma and as the condition becomes severe and chronic, Th1-type T cells are engaged (Truyen *et al.,* 2006). This complicated T-cell profile may explain the aggressive and tissue-damaging aspects of the immune response in severe condition.

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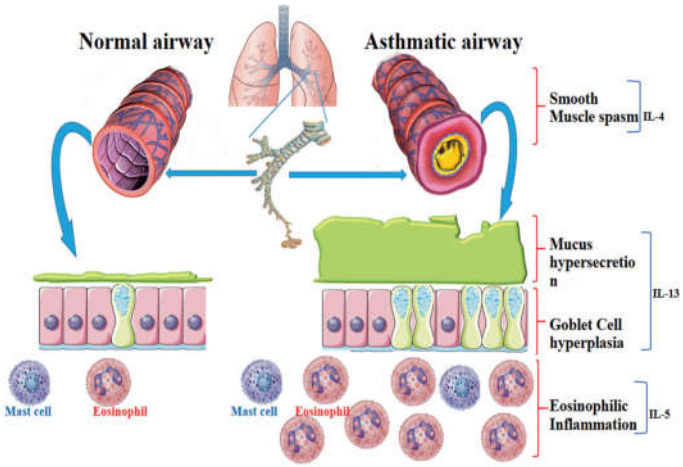
Fig. 3. Morphology and different cell types involved in normal and asthmatic airways-A comparison.



Source: Athari (2019).

In asthma associated with allergic sensitization, the airway recognizes common environmental allergens and generates a Th2 cytokine response to them (Holgate, 2008). Type 2 immune responses in the airway involve accumulation of eosinophils, basophils, mast cells, Th2 cells, Type 2 innate lymphoid cells (ILC2s) and IgE-producing B cells (Oliphant *et al.,* 2011), and cytokines (IL-4, IL-5, and IL-13). All these have a role in pathogenesis of asthma (Dougherty *et al.,* 2009).

At birth: Following birth, infections triggered by environmental allergens will activate ThI response and bring the ThI/Th2 ratio to an appropriate balance. The genetic background of the child, with a cytokine imbalance toward Th2, will enhance the production of IgE antibody in response to environmental antigens. Due to this environment induced gene response, the susceptible host is vulnerable and prone to synthesize IgE molecules where sensitization is manifested (NAEPP, 2002). A comparison of normal and asthmatic airway is represented in Figure 3 (Athari, 2019).

Genetics and asthma: In general, allergic asthma showcase as a genetic disease, since the phenomenon is greater in families with a history of the syndrome (Burrows *et al.,* 1995; Barnes and Marsh, 1998). Asthma is a polygenic, multiplex disorder, so innumerable genes could contribute to it (Thomsen, 2015).

Genetics versus environmental influences in asthma: Genetic predisposition to asthma may exceed environmental effects. The asthma risk, is partially familial in nature, its phenotypic expression may be regulated by genetic and environmental factors (Palmer and Cookson, 2000).

For example, patients with early onset of the disease often have a familial history of asthma than patients with the late disease onset suggesting that genes influence the timing and age for the disease to kick-start (Thomsen *et al.,* 2010).

Asthma-susceptibility genes: Gene-association studies have recognized susceptible genes for asthma using 3 major approaches:

1. Candidate gene studies.
2. Positional cloning using linkage studies.
3. Genome-wide association studies (GWAS).

Asthma susceptibility genes fall into three categories like

1. Immune system function.
2. Maintenance of connective tissues (e.g., matrix metalloproteinases and metallopeptidases) (Melamed and Thomsen, 2017), mucosal tissues and its action.
3. Lung efficiency and disease expression (Vercelli, 2008).

Epigenetic regulation of few genes may be significant, as histone modifications have been associated with bronchial hyper-responsiveness and corticosteroid resistance in asthma (Weiss *et al.,* 2009). Genes for asthma may include ADAM33, Filaggrin, IL-13, HLA-G, GPR154 and many more (De Benedetto *et al.,* 2012; Aierken *et al.,* 2014).

- Candidate gene studies-candidate gene studies emphasize on genes involved in: Th2 inflammation, Regulatory T cell function, the HLA immunity and IgE response of B cells (Postma *et al.,* 2011; Tizaoui *et al.,* 2017), and many other genes and their possible functions as mentioned in Table 5.
- Linkage analysis-Asthma and allergy are controlled by genetic loci acting together which follow Mendelian inheritance at each of these loci. Linkage studies identified few genetic markers causing asthma that are present in chromosomal regions which demonstrate association signals between asthma and novel genetic markers (Jones and Rosenwasser, 2016).
- Genome-wide association studies (GWAS)-Genome-wide association studies, unlike the candidate gene studies, GWAS discover common genetic variations associated with asthma and allergic diseases (Vicente *et al.,* 2017). It screens single nucleotide polymorphisms (SNPs) across the entire genome encoding for the epithelial cell derived cytokines like interleukin-33 (IL-33), thymic stromal lymphopoietin (TSLP) and the IL1RL1 gene encoding IL-33 receptor. These molecules play crucial role in innate immune response pathways and promote the activation and differentiation of Th2 cells and in its pathogenesis (Ober and Yao, 2011).

The effects of associated variation on gene regulation and/or function and of associated genes on asthma pathogenesis and vitality of gene-environment interaction in asthma causation are grave challenges which needs due attention.

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Table 5. Asthma-candidate genes and their functions.

Genes	Chromosome location	Possible functions in asthma phenotypes
Cytokines		
IL-4R	16p11.2-12.1	Promoting the expression of IL-4 sensitive genes, such as IgE
IL-13	5q31	Control eosinophilic inflammation, Ig E dysregulation, stimulating IL-4R, promoting IgE production
IL-17	6p	Overexpressed in mast cells, basophils, CD4+ T cell, induce the production of inflammatory mediators including IL-6, IL-8, TGF-β and ICAM-1, neutrophil recruitment and airway remodeling
Chemokines		
Rantes	17q11.2-q12	Produced by T cells, macrophages, endothelial cells, epithelial cells and mast cells, regulates transcription and protein expression
Immune regulation		
STAT6	12q13.314.1	Signaling cytokines, mediator of inflammation, induces Th2 cell differentiation from naïve T cells and IgE production, regulates the expression of Th2 chemokines
CTLA-4	2q33.2	Expressed on activated T cells,, mediates T cell dependent immune response, inhibiting T cell activation
Homeostasis and airway remodeling		
ADAM33	20p13	Cell adhesion, proliferation, differentiation, intercellular signaling, and apoptosis, inflammatory responses, cleaves extracellular matrix proteins
β2-adrenergic	5q31–32	Cell membrane-spanning β2-adrenergic receptor that binds to epinephrine, mediates smooth muscle relaxation and bronchodilation
Gene-environment interaction		
GSTM1, GSTT1, GSTP1	1p13, 22q11. 2, 11q13	Protective antioxidants in the lung, regulation of inflammatory responses
CD14	5q31.3	Expressed on monocytes, macrophages and neutrophils, binds and neutralizes bacterial endotoxins , stimulates Th1 cytokine expression, suppress Th2 immune responses involved in Ig E-mediated allergic diseases
TLR 2, TLR4, TLR9	4q31-32, 9q 33.1, 3p21.2	Role in host defense against microbes, modulation of the immune system through cellular activation, modulation of cytokine secretion and production of soluble factors to local dendritic networks

Asthma exacerbations

During an asthma attack (asthma exacerbation), the airways become inflamed. Muscle contraction around the airways crop up and it produces extra mucus; causing narrowing of bronchial tubes (GINA, 2019).

The symptoms of an acute exacerbation include:

- Anxiety
- Hyperventilation
- Rapid heart rhythm
- Decreased lung function
- Difficulty in speaking or breathing

Asthma exacerbations are usually life-threatening and a key driver of the economic burden associated with asthma (Rodrigo *et al.,* 2004). During asthma exacerbations there may be a decrease in expiratory airflow as measured with a peak flow meter or spirometry (NAEPP, 2007).

Rates of exacerbations are analogous to the seasons in adults (Johnston and Sears 2006). Despite optimal maintenance therapy and asthma control, exacerbations occur (Castillo, *et al.,* 2017). Asthma exacerbations affect the quality of life (Llyod *et al.,* 2007) and may cause long-term decline in lung function (Krishnan *et al.,* 2006). For patients without exacerbations, health care costs are lower when compared with patients with one or more exacerbation per year (Moore *et al.,* 2007; Sullivan *et al.,* 2007). Some patients with asthma experience exacerbation and few are resistant, supports the heterogeneous nature of asthma. Type 2 immune mechanisms, like arming of plasmacytoid dendritic cells (pDCs) with IgE and increased accumulation of eosinophils in the airway, eventuates susceptibility to exacerbation. Treatments that target IgE and Type 2 cytokines are expected to reduce susceptibility to asthma exacerbations.

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Prevention

Asthmatic patients should plan for living with the condition and prevent susceptibility to asthma exacerbations. Some of the measures are to follow asthma action plan, get vaccinated for influenza and pneumonia (to avoid asthma flare-ups), identify and avoid asthma triggers and monitor breathing and recognize if any warning signs of an impending attack, such as slight coughing, wheezing or shortness of breath. Lung function may decrease before any such signs are exhibited. A regular assessment of peak airflow using a home peak flow meter device measures how hard the patient can breathe out and take prescribed medication and be mindful of increasing use of quick-relief inhaler.

Management

Governments should commit to research programmes that enhances and widens the understanding of asthma, its causes, and improvements in management (Asher *et al.,* 2018). Guidelines from the National Asthma Education and Prevention Program emphasize the following components of asthma care:

1. Assessment and monitoring
2. Education

Key points of education include:

- Type of asthma- its awareness
- Recognize asthma triggering factors
- Choice of medicines and their side effects
- Understanding the differences between relieving and controlling medications
- Knowledge about use of devices
- Self-management and control measures
- Treatment goals to be developed for the patient and family (Bailey *et al.,* 1990; Ignacio-Garcia and Gonzalez-Santos, 1995).

3.Control of environmental factors and comorbid conditions

4. *Pharmacologic treatment:* Patients should be aware of the importance and usage of spacers and valve-holding chambers.

Inhalers: work better and have fewer side effects than tablets.

Long-term controllers: even when there are no symptoms, these can be used daily to keep asthma under check.

Quick –relievers: used only when asthma symptoms occurs. If this type of medication is often used, it means that asthma is not under control.

Nebulizers: converts a drug solution into a fine spray (mist of the medicine) to treat asthma.

Antibiotics: certain bacteria induced respiratory infection in asthma patients causes swelling and mucus that block the airways. In such conditions, antibiotics may be prescribed, to bring down the effect.

Pharmacology guided asthma management

It includes the use of agents for control and relief.

- Inhaled corticosteroids
- Long-acting beta-adrenergic bronchodilators (eg. Medium potency bronchodilators-Theophylline)
- Leukotriene modifiers
- Anti- IgE antibodies (omalizumab)
- Interleukin inhibitors (eg, mepolizumab, benralizumab, dupilumab)

Relief medications include the following:

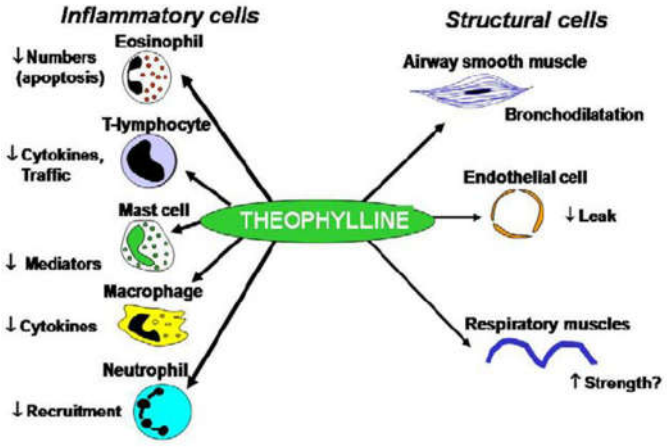
- Short-acting bronchodilators
- Systemic corticosteroids
- Anti-cholinergic agents-Ipratropium

Treating exacerbations

Knowledge of symptoms and speedy intervention can prevent an asthma attack or reduce its severity. The frequency of exacerbations can be reduced, but might not be prevented, with adequate inhaled corticosteroid treatment or in combination with long-acting b-agonists (O'Byrne *et al.,* 2009) and biological therapy in some patients. Exacerbations recur in patients with severe disease and prevention with anti-IgE and anti-IL-5, may help. Bronchodilator therapy may not be effective during exacerbations and in such situation, administration of systemic corticosteroids remains the primary intervention, but they have limitations.

Long-acting bronchodilators: Long-acting beta-adrenergic bronchodilators like theophylline are used daily and long-term for preventing bronchospasm, exercise-induced asthma, asthma attacks or for reducing the frequency of symptoms (Barnes, 2010 a) (Fig. 4).

Fig. 4. Effect of bronchodilator-theophylline on structural and inflammatory cells in treating asthma.



Source: Barnes (2010a).

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Short-acting b2-agonists (SABAs): Short-acting b2-agonists have no effect on airway inflammation but can provide symptomatic relief. Nebulized short-acting b2-agonists, such as albuterol or levalbuterol, relieve acute symptoms of asthma and can be used every 15 to 20 minutes for the first hour (Rodrigo and Rodrigo, 1999; Kelly, 2007). These agonists usually inhibit the release of mast cell mediators and sensory nerve activation. Based on improved pulmonary function (reducing the frequency of hospitalisations), in severe asthma exacerbations, continuous nebulization should be considered (Camargo *et al.*, 2009).

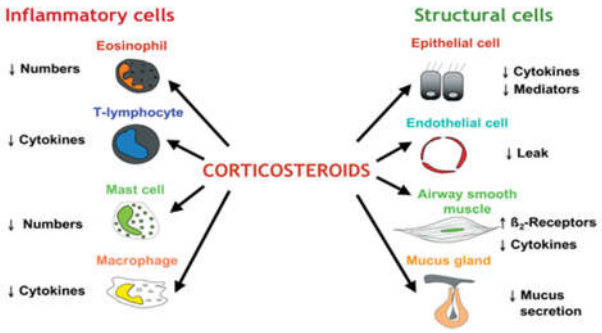
Anti-cholinergic agents-Ipratropium bromide: Ipratropium bromide opens up the medium and large airways in the lungs and prevents cholinergic nerve induced bronchoconstriction. It can block receptors on bronchial smooth muscles. Since it is less effective than b2-agonists, it is administered in combination with an inhaled SABA, thereby decreases rate of hospitalizations for patients with severe or moderate-to-severe asthma exacerbations (Krishnan *et al.*, 2009).

Corticosteroids- Inhaled Corticosteroids (ICS) and oral corticosteroids (OCS): An increase in airway inflammation is the fundamental cause of exacerbations. Common treatment for acute asthma flare-ups is to reduce inflammation and swelling in the airways thereby improving the lung function. Corticosteroids prophylactically can be used as controller therapy. It modulates cytokine and chemokine production (Fig. 5) (Barnes, 2010b). These OCS have been shown to decrease emergency hospitalizations. Inhaled steroids are the mainstay treatment for controlling asthma, but do not prevent exacerbations.

Anti-IgE: Inspite of moderate-to-high dose ICS, if patients possess persistent asthma, then Omalizumab, a humanized monoclonal antibody directed against IgE may be recommended. It acts on the allergic arm of the immune system. IgE bound to Omalizumab cannot bind to IgE receptors on mast cells and basophils, hence preventing the allergic reactions. So it can be used at early stages of treatment (Pelaia *et al.*, 2011) (Fig. 6). In addition to ICS, Omalizumab is given to lessen and shorten the asthma exacerbations (Ohta *et al.*, 2009; Hanania *et al.*, 2013).

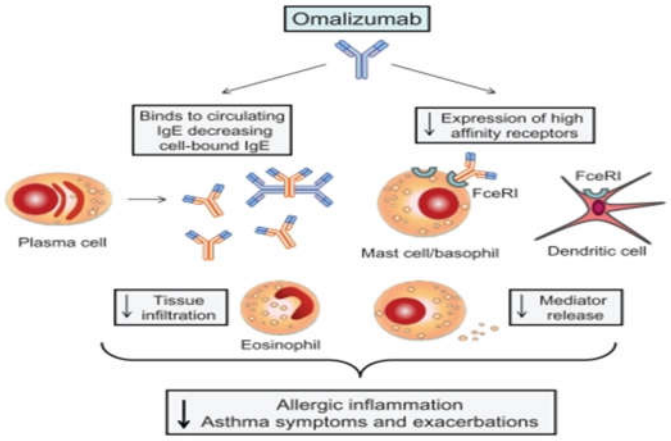
Anti-IL-5: Interleukin-5 (IL-5) contributes to airway eosinophilic inflammation. New therapies targeting (IL-5) to treat severe eosinophilic asthma are the possible emerging alternatives. Two anti-IL-5 monoclonal antibodies, Mepolizumab and reslizumab provide remarkable and clinically admissible improvements in exacerbation rate and OCS reduction (Pavord *et al.*, 2012, Porsbjerg *et al.*, 2018).

Fig. 5. Effect of corticosteroids on different cell types in the treatment of asthma.



Source: Barnes (2010b).

Fig. 6. Action of anti-IgE (Omalizumab) on allergen sensitized immune cells.



Source: Pelaia *et al.* (2011).

Asthma Management-India's Perspective

Increased cost of living, wide gap in the quality of available healthcare facilities for affordable and non-affordable section, lack of health insurance among low income population and the inability of government in assuring a minimum health insurance coverage at least to low income population if not to all citizens puts the risk rate for asthma little higher in India and even more in women. Most of the available drugs in market like inhaled corticosteroids; β2-agonist and combination inhalers are expensive in comparison to oral formulations (Bissell *et al.*, 2018, El Sony *et al.*, 2018). In 2015, the Indian Chest Society and National College of Chest Physicians published Indian asthma guidelines. In addition to implementing these guidelines, strengthening of awareness driven education policy and encouraging the use of self-management strategies and more country-specific research oriented programmes for novel therapies are need of the hour. This kind of approach certainly would help to target and deliver a better, standardized, affordable patient specific asthma health care to all in future.

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Conclusion

Epidemiological studies reveal that environment could be a crucial factor in influencing epigenetics and thereby unraveling additional mechanisms, novel approaches and targets to the treatment. The application of advanced and next generation cell and molecular biology tools to different observed phenotypes of asthma patients at different points in their natural history might also eventually, unveil and address the possible causes of atopy and its occurrence in some individuals which later evolves into asthma. Asthma is a heterogeneous syndrome consisting of several immunological subtypes with differing disease mechanisms, which has opened an avenue for patient specific pharmacological treatment. Patients need to learn that ICS are not addictive or dangerous. People with symptoms should first contact their health centres for assessment, so an effective network of responsible, trained health professionals, in combination with adherence to formulated guidelines, is essential to overcome and cure asthma.

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