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BRONCHIAL ASTHMA: AN UNMET DISEASE

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ABSTRACT: Asthma is a chronic obstructive disease of airways affecting bronchi, resulting in bronchoconstriction, tightening of chest and airway inflammation. Asthma remains a disease with clearly unsatisfactory therapeutics. With the mounting evidence in support of asthma being an inflammatory illness, anti-inflammatory agents have now become prerequisite for the long-term management of asthma. Along with anti-inflammatory agents, there is a need to search for other effective therapies to treat every aspect of the disease. The present review gives an insight of various approaches available for the management of asthma. A number of drugs are available with chemical diversity as on date for the treatment of bronchospasmolytic conditions. The different sites or receptor involved in this intervention is adrenoceptor, steroid receptor, phosphodiesterase and many more. The agents such as β-agonist, antihistaminics, anticholinergics and inhalation steroids, only treat symptoms and do not cure the underlying inflammation. On the other hand, adenosine receptor modulators, selective PDE4 inhibitors, leukotriene modifiers and lipoxygenase inhibitors represents other therapeutic interventions with more targeted control by acting on different parts of immune system and the inflammatory processes. A combination of both of these approaches has been found to improve asthma control with a reduced dose of steroids. With many representative agents of each of these potential therapeutic targets, undergoing clinical studies, successful development of novel therapeutic agents in this field, is not remote. There is a need to understand completely about the phenotype of asthmatic patients so that each patient will receive proper therapy.

INTRODUCTION: Health as given by WHO (1946) is "a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity." The ability to make logical and effective interventions into people's health is a new ethical responsibility too as health care resources are limited and distributed appropriately. The literature reveals that the new clinical diagnoses are often welcomed as opportunities for the growth of pharmaceutical market. [1]

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Asthma and the complications due to it, have great impact on the quality of life. [2] There are no specific strategies and realistic options available to completely cure asthma so the main emphasis is to control the manifestations of the disease. [3, 4]

According to recent GINA (Global Initiative for Asthma) strategy, asthma control is based on assessing the symptom control and the risk factors associated with its poor outcome. [5] Global Asthma Report 2014 reported about 334 million people suffered from asthma and this figure was projected to escalate to 400 million by the year 2025. Asthma is reported as the 14th most important disease in the world according to statistics and it affects about 14%, 8.6% and 4.5% of world children, young adults and world population, respectively. [6-8]

Among the total asthma cases globally, about 5% to 10% account for severe uncontrolled asthma.[9-10] The cost of direct and indirect asthma in controlled and uncontrolled asthma patients between the age group 15-64, was estimated to be €19 billion/annum.[11]

Asthma: Asthma is described as a chronic obstructive inflammatory disease consisting of a cellular component which results in the inflammation of airways and hyper-responsiveness in response to some direct or indirect stimuli. [12] The symptoms include recurrent episodes of wheezing, breathlessness, chest tightening and coughing, particularly at night or in the early morning.

The airflow limitation due to smooth muscle contractions, edema and hypersecretion, is responsible for airway tissue reactions. [13] The various drug management groups such as the National Institutes of Health (USA), the Global Initiative for Asthma (GINA) and the Japanese Society of Allergology (JSA) have published several asthma prevention and management guidelines. [14-18]

Epidemiology: Asthma is a common medical condition that affects 300 million people worldwide and 25 million people in United States with that number expected to rise. [19] It is considered as one of the costlier chronic condition, with an estimated 15 million daily-adjusted life years (DALYs) lost annually and results in one of every 250 deaths worldwide. The survey on disease is defined as current episodes of wheezing or a physician's diagnosis shows that asthma usually affects 5-16% of the people worldwide. [20] The rate of disease varies in different countries depending upon the diagnostic standards. [21]

The documented increase in asthma in last 25 years is due to the changes in our lifestyle and environment as genetic changes take place in years. [22] As asthma rates are increasing almost 50% every decade, it is found to be the third leading cause of death by 2020 according to World Health Organization (WHO). The rates of asthma are higher among developed countries, [23-29] most of the people acquire them before 10 years of age while others acquire by the age of 30 (**Table 1**).[24-28]

TABLE 1: PREVALENCE OF ASTHMA IN DIFFERENT COUNTRIES

Country	Prevalence/1000
Scotland	184
U.K.	153
New Zealand	151
Australia	147
Canada	141
U.S.A.	130
Brazil	114
Pakistan	108
Turkey	74
France	68
Japan	67
Thailand	65
Germany	63
Iran	55
Nigeria	54
Malaysia	48
Italy	45
India	24
Russia	22
China	21
Macau	07

Types of Asthma: Asthma may be triggered by a number of factors such as mold, dust, pets, cockroach, certain chemical odors, smoke, grass, weeds etc. Depending on the age and the factors involved, asthma can be classified as:

1. Childhood Asthma
2. Adult onset Asthma
3. Exercise induced Asthma
4. Cough induced Asthma
5. Occupational Asthma
6. Nocturnal Asthma
7. Steroid resistant Asthma

In certain cases, the first symptoms of asthma are usually seen during the preschool years and even those who develop chronic symptoms at young age, episodic wheezing and bronchial hyper-responsiveness were detected early in life. [30] The strongest predictor of continued and increasingly severe symptoms is chronic airflow limitation and includes three phases:

A Prenatal phase [31-34]
A Preschool phase [33, 35]
A Phase lasting throughout the lifetime [36, 37]

The postnatally acquired airflow obstruction is usually seen in patients with recurrent exacerbations. The lung function impairment is

also associated with occupational asthma and exposure to air pollution. [38, 39] Some children show only mild, transient and sporadic episodes of airway obstruction that does not lead to chronic asthma. Depending upon the severity of asthmatic episodes, it can be further classified as in **Table 2**.

TABLE 2: CLASSIFICATION OF ASTHMA

Classification of Asthma	
Mild Intermittent	Attacks not more than twice a week and night time attacks not more than twice a month. Attacks last for few hours and severity of attack varies.
Mild Persistent	Attacks more than twice a week and night time symptoms more than twice a month. Sometimes attacks are severe enough to interrupt regular activities.
Moderate Persistent	Daily attacks, Night time symptoms more than once in a week. Severe attacks at least twice a week lasting for days. Attacks require daily use of rescue medication and changes in daily activities.
Severe Persistent	Frequent severe attacks, continual daytime symptoms and frequent night time symptoms. Symptoms require limits on daily activity.

Signs and Symptoms: The susceptibility to asthma seems to be associated with microbial colonization of airways. The infants who have been detected with increased amounts of pathogenic bacteria in upper airways, found to develop symptoms of asthma in preschool years. [40] The various signs and symptoms associated with asthmatic attacks are:

Coughing, especially at night, during exercise and laughing
Wheezing (whistling or squeaky sound in chest while breathing, especially when exhaling)
Shortness of breath
Tightness in chest
Pain and pressure in chest

The symptoms of asthma may be triggered by exposure to certain allergens such as weeds, pollen, pets, dust, mites etc. or due to the presence of some irritants in air such as smoke, chemical irritants or certain odors or due to some extreme weather conditions or the presence of sulfites in certain food stuffs. Certain conditions like respiratory illness, exercise and flu makes a person more susceptible to asthmatic attack. A strong display of certain emotions such as shouting, crying, laughing may sometime also contributes towards asthmatic attack. The researchers have found that breathing pattern associated with strong emotions can lead to the constriction of bronchial tubes, provoking or worsening of an attack. Asthma, like other chronic conditions lead to emotional stress. The inability to work and school absences affects the livelihood, educational and emotional well-being, resulting in depression.

All the asthmatic patients do not show above mentioned symptoms and similarly, the presence of above symptoms does not indicates that a person is suffering from asthma. The diagnosis of asthma is done by the medical history of person, physical examination, lung function test and positive methacholine challenge test.

Pathophysiology of Asthma:

Cells and Cytokines: Bronchial Asthma (BA) is a typical allergic disease and the mechanism involved is being searched widely. The previous studies concluded that asthma is T-helper-type-2 (Th2)-cell dependent IgE mediated allergic disease as most of asthmatics are sensitive to aeroallergens. [41] The characterization of pathological basis of asthma includes mucus cell hyperplasia and infiltration of inflammatory cells that includes CD4+ T cells, eosinophils and mast cells. The classical model of asthma is a complex web of cells and the cell signaling molecules interact with each other to elicit an inflammatory response. The Allergen/Antigen presentation by antigen presenting cells (APC) to T-helper-type-0 cells (Th0) leads to the differentiation of Th2 cells. The antigen stimulation results in the production of thymic stromal lymphopoietin (TSLP) in the epithelial cells of airways.

TSLP acts upon its receptors (TSLPR) which are expressed by dendritic cells (DCs) and promotes the transcription of OX-40L, a member of TNF (Tumor Necrosis Factor) family of cytokines. OX-40L by the help of activated DCs induces expression of Th2 cytokines resulting in differentiation of inflammatory Th2 cells. [42] The inflammatory Th2 cells then produce various types of cytokines as IL-4, IL-5 and IL-13. These cytokines activate B-cells resulting in the synthesis and release of immunoglobulin IgE.

The inhaled allergens bind to the receptors present on the surface of mast cells where IgE also binds to release various inflammatory mediators such as histamine, prostaglandin and leukotrienes by degranulation. These chemical inflammatory mediators acts as cell signaling molecules to induce bronchoconstriction of smooth muscles, airway obstruction and further propagates the inflammatory response (**Fig. 1**). Th2 lymphocytes also produce another class of cytokines, IL-9 which also stimulates the proliferation of mast cells in airways [43] and IL-5 which is associated with the survival of eosinophils. [44] Eosinophils also participate in the inflammatory process by releasing the inflammatory chemical mediators like Leukotrienes and Reactive Oxygen Species (ROS) resulting in bronchoconstriction, mucous secretion and structural damage to airways. [45-48] The patients with Th2 cytokines and eosinophil predominant-asthma responds well to Inhaled Corticosteroids (ICS).The ones with high eosinophil-predominance are responsive to treatment with anti-IL-5 antibody.

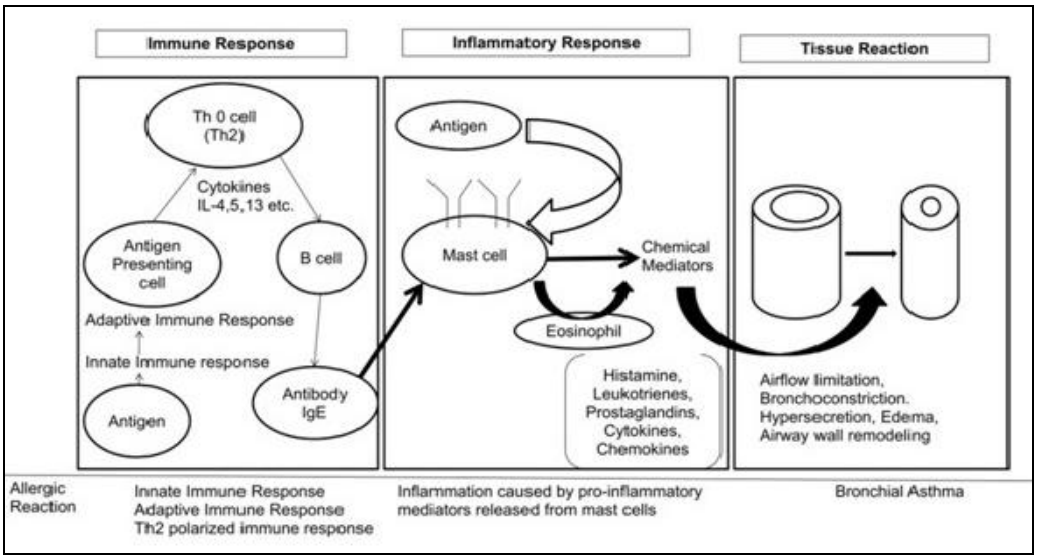

FIG. 1: PROCESS OF ALLERGIC ASTHMA

Along with Th2 cytokines and eosinophils, asthma is also related to neutrophil-predominant Th17 associated disease as Th17 and it is associated IL-17 cytokines also play significant role in airway inflammation. The presentation of antigen presenting cells (APC) by IL-23 results in the differentiation of Th17 cytokines. The expression of IL-17 by Th17 cells augments *in vitro* glucocorticoid beta (GR-β) expression by epithelial cells of airways. GR-β acts by the competitive inhibition of GR-α mediated anti-inflammatory gene transcription at glucocorticoid response element (GRE).[49]

IL-17 helps in the recruitment of neutrophils by releasing IL-8 from epithelial cells of airways and is also an activator of endothelial cells to promote transmigration of neutrophils at the site of inflammation.[50] Airway neutrophils produces various lipid mediators like elastase, leukotriene-B4 and matrix metalloproteinase-9 (MMP-9) and platelet activating factors (PAF), all of which further propagates the process of inflammation and also recruits eosinophils. [51] Airway epithelial cells also release IL-5 and a stem cell factor (SCF), a cytokine supporting the survival of mast cell within airways, and a macrophage chemo-attractant protein-1 (MCP-1). MCP-1 also recruits alveolar macrophages thus enhancing the inflammatory process. On binding of allergen to IgE receptors, these macrophages release certain cytokines such as IL-1β, TNF-α and IL-6 and elastase (degrade elastin in airway extracellular matrix) and metalloproteinase. [52, 53] These cytokines further act on epithelial cells and releases Granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8 and regulated on activation, normal T cells expressed and secreted (RANTES). GM-CSF and RANTES recruits eosinophils and promote their survival in airways.[54, 55]

One more type of immune regulatory myeloid derived cells also play a role as regulators of allergic inflammation. During inflammation, the

oxidative stress regulates expansion, activation, recruitment and function of these myeloid cells. The differential regulation by NO (nitric oxide) produces immature myeloid cells which gives their contribution in the balance of immune suppression and exacerbation of the hyper-responsiveness of airways (**Fig. 2**).[56]

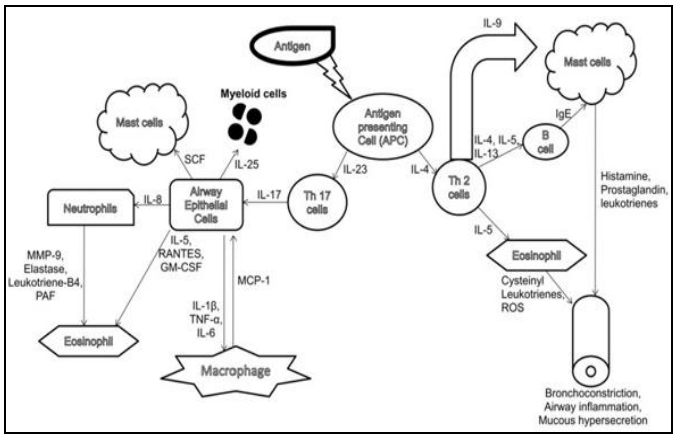

FIG. 2: PATHOGENESIS OF ASTHMA

Airway Remodeling: Inflammation results into a number of structural changes in airways including the thickening of basement membrane, subepithelial fibrosis, metaplasia of goblet cells, neovascularization and increased smooth muscle mass of airways. All asthmatic patients experience serious effects on the structure and function of airways, regardless of the duration of disease. Airway remodeling is usually associated with an irreversible decrease in forced expiratory volume (FEV1), increase in the hyper-responsiveness of airways, increase in the thickness of basement membrane of airways and loss of bronchodilator reversibility. [57, 58]

Furthermore, all these structural changes in the airways of asthmatics help in the development and progression of disease. It is unclear whether the inflammation precedes or coexists with airway remodeling but remodeling can occur early in the disease even in the absence of inflammation. There is a direct relationship between mechanical stress and airway remodeling in asthma.[59]

Methods for the treatment of asthma: The previous studies about the pathophysiology of asthma suggests various available targets whose activation or blockade will be beneficial to treat asthma. The various available approaches are:

Prevention of antigen-antibody reaction: Antigen avoidance, hyposensitization

Neutralization of IgE (reaginic antibody): Omalizumab

Prevention of the release of mediators: Mast cell stabilizers

Suppression of inflammation and bronchial hyper-reactivity: Corticosteroids

Antagonism of released mediators: Leukotriene antagonist, Antihistamines, PAF antagonists.

Blockade of constrictor neurotransmitter: Anticholinergics

Mimicking dilator neurotransmitter: Sympathomimetics

Directly acting bronchodilators: Methylxanthines

Adenosine modulators: Based on above approaches, antiasthmatics can be classified pharmacologically into various classes, broadly as bronchodilators and corticosteroids which can be classified further. The chemical structures of various antiasthmatic drugs available in market are given in **Fig. 3**

Bronchodilators:

1. β_2-sympathomimetics (Salbutamol, Terbutaline, Bambutarol, Salmeterol, Formoterol, Ephedrine)
2. Methylxanthines (Theophylline, Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Doxophylline)
3.Anticholinergics (Ipratropium bromide, Tiotropium bromide)

Leukotriene Antagonist (Montelukast, Zafirlukast)

Mast cell stabilizers (Sodium Cromoglycate, Ketotifen)

Corticosteroids:
1. Systemic Corticosteroids (Hydrocortisone, Prednisolone)
2. Inhalational Corticosteroids (Beclomethasone, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide)

Anti IgE antibody (Omalizumab)
Miscellaneous drugs (Prostaglandins, Antihistamines, Adrenocorticotropic hormone)

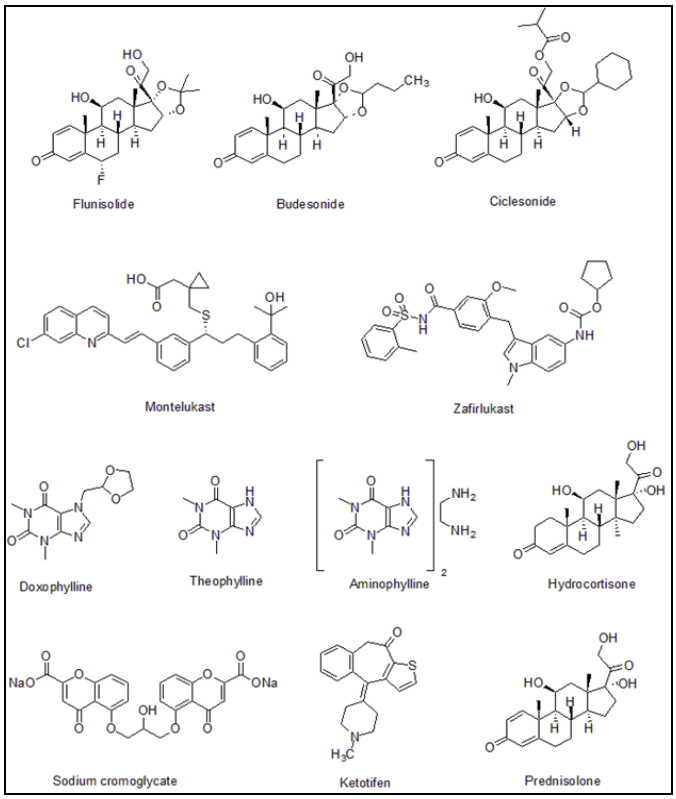

FIG. 3: VARIOUS ANTIASTHMATIC DRUGS

RESULTS AND DISCUSSION: There is no strategy to prevent primary asthma and to prevent the limitation of airflow in asthmatics. The avoidance of allergens even during pregnancy and early infancy has no effect on outcomes of asthma. The two important aspects to treat asthma are: Environmental Control and Pharmacological Therapy. The under developed countries face troubles in terms of under diagnosis, availability and affordability to therapy which in turn is associated with increased rate of mortality and morbidity associated with asthma and requires extensive care. [60]

The main causative agent is environmental exposure but still the treatment in terms of allergen avoidance is controversial. The pharmacological therapy includes the use of inhaled corticosteroids with or without long acting beta agonists, leukotriene receptor antagonists, anti IgE antibody, antibodies against chemokines and cytokines, phosphodiesterase inhibitors, antihistamines and thermoplasty.

α-adrenoceptor blockers decreases histamine induced bronchoconstriction but they also have antihistaminic activity or direct smooth muscle relaxing activity so the exact observation is hard to interpret. The β-adrenoceptor stimulation of bronchial muscles releases bronchial spasm and inhibits the liberation of inflammatory mediators. Xanthines act by inhibiting the enzyme phosphodiesterase (PDE) resulting in bronchodilation by relaxing the smooth muscles. Thus, there is a need for the introduction of novel therapies which are targeted specifically against components of inflammatory pathway. The three major approaches for the development of newer anti-asthmatic drugs are: improvement of existing class of effective drugs (ICs and LABAs but have systemic side effects), development of novel compounds and serendipity development. The anti-allergy drugs also acts as another approach to inhibit allergen induced diseases.

CONCLUSION: Currently, a number of approaches are available for asthma but still from past 30 years only few drugs are able to make their way till market. Thus, there is a need to understand completely the exact phenotype of asthmatic patients so that each patient will receive proper therapy and also maximize the pathway for the development of newer drugs. A number of sites or receptors are involved in the progression of disease so the complete understanding of each receptor and the mechanism involved will give a clear view about the therapy to be followed whether alone or in combination with one or more class of drugs. Thus, there is a need to broaden the area of research and to focus on other potential therapeutic agents for the treatment of asthma which not only gives symptomatic relief but also cure the disease. The increased knowledge and complete understanding of the disease will hopefully lead to still more effective remedies for asthma. The present demand is to spread the knowledge of existing therapeutic possibilities.

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REFERENCES:

1. Cassels A and Welch G: Seeking Sickness: Medical Screening and the Misguided Hunt for Disease. Greystone Books, 2012.
2. Pereira ED, Cavalcante AG, Pereira EN, Lucas P and Holanda MA: Asthma control and quality of life in patients with moderate or severe asthma. Brazilian Journal of Pulmonology 2011; 37: 705–711.
3. Bateman ED, Hurd SS and Barnes PJ: Global strategy for asthma management and prevention: GINA executive summary. European Respiratory Journal 2016; 31: 143–78.
4. Chung KF, Wenzel SE, Bronzek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL and Teague WG: International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European Respiratory Journal 2014; 43: 343-373.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2014.
6. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C and Bridgett L: Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2013; 380: 2197-2223.
7. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA and Boulet LP: Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012; 12: 204-208.
8. Global Asthma Report (2014). Auckland, New Zealand: Global Asthma Network, 2014.
9. Al-Hajjaj MS: Difficult-to-treat asthma, Is it really difficult? Annals of Thoracic Medicine 2011; 6: 1-6.
10. Dheda K, Koegelenberg CFN, Esmail A, Irusen E, Wechsler ME, Niven RM and Chung KF: Recommendations for the use of bronchial thermoplasty in the management of severe asthma. South African Medical Journal 2015; 105: 726-732.
11. Domínguez-Ortega J, Phillips-Anglés E, Barranco P and Quirce S: Cost effectiveness of asthma therapy: A comprehensive review. Journal of Asthma 2015; 52: 529-537.
12. Trevor JL and Deshane JS: Refractory asthma: mechanisms, targets, and therapy. Allergy 2014; 69: 817–827.
13. Nagai H: Recent research and development strategy of anti-asthma drugs. Pharmacology and Therapeutics 2012; 133: 70–78.
14. O'Byrne PM: Global guidelines for asthma management: summary of the current status and future challenges. Polish Archives of Internal Medicine 2010; 120: 511–517.
15. Hoeksema LJ, Bazzy A, Lemotan EA, Edmonds DE, Ramirez-Garnica G and Shiffman RN: Accuracy of a computerized clinical decision-support system for asthma assessment and management. Journal of American Medical Informatics Association 2011; 18: 243–250.
16. Moore WC and Pascual RM: Update in asthma 2009. American Journal of Respiratory and Critical Care Medicine 2010; 181: 1181–1187.
17. Dahlén SE, Dahlén B and Drazen JM: Asthma treatment guidelines meet the real world. The New England Journal of Medicine 2011; 364: 1769–1770.
18. Ohta K, Yamaguchi M, Akiyama K, Adachi M, Ichinose M and Takahashi K: Japanese guideline for adult asthma. Allergology International 2011; 60: 115–145.
19. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA and Boulet LP: Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012; 12: 204.
20. Akinbami LJ, Moorman JE and Bailey C: Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. Hyattsville, MD, USA: National Center for Health Statistics, 2012.
21. Asher MI, Montefort S and Bjorksten, B: Worldwide time trends in the prevalence of symptoms of asthma, allergic rhino conjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006; 368: 733–743.
22. Covar RA, Strunk R and Zeiger RS: Predictors of remitting, periodic, and persistent childhood asthma. Journal of Allergy and Clinical Immunology 2010; 125: 359–366.
23. Ichinose M: Differences of Inflammatory mechanisms in Asthma and COPD. Allergology International 2009; 58: 307-313.
24. Ko YA, Song PXK and Clark NM: Declines With Age in Childhood Asthma Symptoms and Health Care Use. Health Education and Behavior 2014; 41: 539-549.
25. Tagiyeva N, Devereux G, Fielding S, Turner S and Douglas G: Outcomes of Childhood Asthma and Wheezy Bronchitis. A 50-Year Cohort Study. American Journal of Respiratory and Critical Care Medicine 2016; 193: 23-30.
26. Chan JYC, Stern DA, Guerra S, Wright AL, Morgan WJ and Martinez FD: Pneumonia in Childhood and Impaired Lung Function in Adults: A Longitudinal Study. Pediatrics 2015; 135: 607-616.
27. Bisgaard H, Jensen SM and Bonnelykke K: Interaction between asthma and lung function growth in early life. American Journal of Respiratory and Critical Care Medicine 2012; 185: 1183–1189.
28. Mullane D, Turner SW and Cox DW: Reduced Infant Lung Function, Active Smoking, and Wheeze in 18-Year-Old Individuals. JAMA Pediatrics 2013; 167: 368-373.
29. Bernstein JA and Levy ML: Clinical Asthma: Theory and Practice. CRC Press, Taylor and Francis Group, New York, 2014.
30. Tai A: Strengths, Pitfalls, and Lessons from Longitudinal Childhood Asthma Cohorts of Children Followed Up into Adult life. BioMed Research International 2016; 2016:1-8.
31. Haland G, Carlsen KC and Sandvik L: Reduced lung function at birth and the risk of asthma at 10 years of age. The New England Journal of Medicine 2006; 355: 1682–1689.
32. Stern DA, Morgan WJ, Wright AL, Guerra S and Martinez FD: Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet 2007; 370: 758–764.
33. Bisgaard H, Jensen SM and Bonnelykke K. Interaction between asthma and lung function growth in early life. American Journal of Respiratory and Critical Care Medicine 2012; 185: 1183–1189.
34. Turner SW, Palmer LJ and Rye PJ: The relationship between infant airway function, childhood airway responsiveness, and asthma. American Journal of Respiratory and Critical Care Medicine 2004; 169: 921–927.
35. Morgan WJ, Stern DA and Sherrill DL: Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. American Journal of Respiratory and Critical Care Medicine 2005; 172: 1253–1258.

36. Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS and Szefler SJ: Mild to moderate asthma affects lung growth in children and adolescents. Journal of Allergy and Clinical Immunology 2006; 118: 1040–1047.
37. James AL, Palmer LJ and Kicic E: Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. American Journal of Respiratory and Critical Care Medicine 2005; 171: 109–114.
38. Mortimer K, Neugebauer R, Lurmann F, Alcorn S, Balmes J and Tager I: Air pollution and pulmonary function in asthmatic children: effects of prenatal and lifetime exposures. Epidemiology 2008; 19: 550–557.
39. Anees W, Moore VC and Burge PS: FEV1 decline in occupational asthma. Thorax 2006; 61: 751–755.
40. Bisgaard H, Hermansen MN and Buchvald F: Childhood asthma after bacterial colonization of the airway in neonates. The New England Journal of Medicine 2007; 357: 1487–1495.
41. Burrows B, Martinez FD, Halonen M, Barbee RA and Cline MG: Association of asthma with serum IgE levels and skin test reactivity to allergens. The New England Journal of Medicine 1989; 320: 271–277.
42. Liu YJ: Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell-mediated allergic inflammation. Journal of Allergy and Clinical Immunology 2007; 120: 238–244.
43. Barnes PJ: The cytokine network in asthma and chronic obstructive pulmonary disease. The Journal of Clinical Investigation 2008; 118: 3546–3556.
44. Adcock IM and Caramori G: Cross-talk between pro-inflammatory transcription factors and glucocorticoids. Immunology and Cell Biology 2001; 79: 376–384.
45. Gleich GJ: Mechanisms of eosinophil-associated inflammation. Journal of Allergy and Clinical Immunology 2000; 105: 651–663.
46. Porsbjerg CM, Gibson PG, Pretto JJ, Salome CM, Brown NJ and Berend N: Relationship between airway pathophysiology and airway inflammation in older asthmatics. Respirology 2013; 18: 1128–1134.
47. Niimi A: Cough, asthma and cysteinyl leukotrienes. Pulmonary Pharmacology and Therapeutics 2013; 2: 514–519.
48. Annema JT, Sparrow D, O'Connor GT, Rijcken B, Koeter GH and Postma DS: Chronic respiratory symptoms and airway responsiveness to methacholine are associated with eosinophilia in older men: the Normative Aging Study. European Respiratory Journal 1995; 8: 62–69.
49. Vazquez-Tello A, Halwani R, Hamid Q and Al-Muhsen S: Glucocorticoid receptor-beta up-regulation and steroid resistance induction by IL-17 and IL-23 cytokine stimulation in peripheral mononuclear cells. Journal of Clinical Immunology 2013; 33: 466–478.
50. Roussel L, Houle F, Chan C, Yao Y, Berube J and Olivenstein R: IL-17 promotes p38 MAPK-dependent endothelial activation enhancing neutrophil recruitment to sites of inflammation. Journal of Immunology 2010; 184: 4531–4537.
51. Nakagome K, Matsushita S and Nagata M: Neutrophilic inflammation in severe asthma. International Archives of Allergy and Immunology 2012; 15: 96–102.
52. Bousquet J, Chanez P, Lacoste JY, White R, Vic P and Godard P: Asthma: a disease remodeling the airways. Allergy 1992; 47: 3–11.
53. Howell CJ, Pujol JL, Crea AE, Davidson R, Gearing AJ and Godard P: Identification of an alveolar macrophage-derived activity in bronchial asthma that enhances leukotriene C4 generation by human eosinophils stimulated by ionophore A23187 as a granulocyte-macrophage colony-stimulating factor. The American Review of Respiratory Disease 1989; 140: 1340–1347.
54. Adcock IM and Caramori G: Cross-talk between pro-inflammatory transcription factors and glucocorticoids. Immunology and Cell Biology 2001; 79: 376–384.
55. Barnes PJ: Similarities and differences in inflammatory mechanisms of asthma and COPD. Breathe 2011; 7: 229-238.
56. Deshane J, Zmijewski JW, Luther R, Gaggar A, Deshane R and Lai JF: Free radical-producing myeloid-derived regulatory cells: potent activators and suppressors of lung inflammation and airway hyper responsiveness. Mucosal Immunology 2011; 4: 503–518.
57. Pascual RM and Peters SP: The irreversible component of persistent asthma. Journal of Allergy and Clinical Immunology 2009; 124: 883–890.
58. Shifren A, Witt C, Christie C and Castro M: Mechanisms of Remodeling in Asthmatic Airways. Journal of Allergy 2012; 2012: 1-12.
59. Nagatomi J: Mechanobiology Handbook. CRC Group, Taylor and Franchis Group, New York, 2011.
60. Zar HJ and Levin ME: Challenges in treating pediatric asthma in developing countries. Paediatric Drugs 2012; 14: 353–359.

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