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# Immunology in the Management of Asthma for Children, Adolescents and Adults

**Andrew Kiboneka[1]* and Kibuule Dan[2]**

[1]*Department of Paediatrics, School of Medicine, Faculty of Health Sciences, University of Namibia, Namibia*

[2]*Department of Pharmacy Practice and Policy, School of Pharmacy, Faculty of Health Sciences, University of Namibia, Namibia*

***Corresponding Author:** Andrew Kiboneka, Department of Paediatrics, School of Medicine, University of Namibia, Windhoek, Namibia.

**Received:** June 13, 2019; **Published:** August 26, 2019

## Abstract

**Background:** Asthma is a rising public health burden in developing countries in sub-Saharan Africa. The integration of immunotherapeutic interventions for asthma remains limited despite the burden of disease in the sub-Saharan Africa. Asthma remains underdiagnosed and under-treated, leading to poor quality of life, and enormous social, family and economic costs.

**Aim:** To review the potential clinical application and usefulness of immunology and machine learning in the diagnosis and management of asthma in sub-Saharan Africa.

**Methods:** The study was a systematic review of the evolution of asthma management to provide guidance for asthma treatment and policies in sub-Saharan Africa. The search strategy included all articles published in English between January 2008 and December 2018. The search terms were advances in case definition, classification (i.e. phenotypes and endo-types) and heterogeneity of asthma. In addition, we reviewed immune cells, biomarkers, and the role of the epithelium plus biological agents in the management of severe asthma in children, adolescents and adults.

**Findings:** The management of asthma has evolved from concepts of clinical symptoms and signs to immunological phenotyping based on biomarkers, especially for severe asthma across all patient populations. Nevertheless, there is limited access to current optimal recommended asthma interventions in sub-Saharan Africa.

**Conclusions:** There is a dire need to introduce biomarkers and phenotyping for the diagnosis of severe asthma in sub-Saharan Africa and thus have precision based medicine for Asthma.in this region to decrease morbidity and mortality of Asthma in children, adolescents and Adults.

***Keywords:*** *Asthma; Immunology; Classification; Phenotypes; Asthma Management; Sub Saharan Africa*

## Introduction

The role of immunology in medical practice is not new and dates from the 18th century when Edward Jenner initiated immunization. In an eight year old boy. Since then, immunization has improved global public health and saved more lives than any other medical advance. In 19th and 20th centuries, the understanding immunology led major scientific breakthroughs such as organ transplants, blood typing, and the clinical application of monoclonal antibodies in healthcare. Similarly, immunological research remains a major tool for diagnosis and treatment of asthma, autoimmune diseases as well as discovery of vaccines for emerging pathogens, such as Ebola.

Asthma is a rising global public health burden especially in the developing countries. Study of Asthma and Allergies in Children (ISAAC) reports a significant increase in the global prevalence of asthmatic episodes among children [1,2]. This increase in reporting of asthmatic episodes possibly reflects a greater awareness of Asthma. Similarly, the increase asthmatic episodes, morbidity and mortality among populations in Africa, Latin America and parts of Asia is a rising public health concern [3,4]. Asthma is a chronic inflammatory disease of the conducting airways in which many cells of the innate and adaptive immune systems act together with epithelial cell. Asthma is a disease of increased airway hyperresponsiveness and airflow limitation that is increasingly being viewed as a heterogeneous syndrome composed of an assortment of disease subtypes with differing causes and natural Nevertheless, the development of new asthma phenotyping and treatment including machine learning and big data have markedly improved treatment outcomes. In particular, the reclassification of severity of asthma as well as novel treatment options based on immunological biomarkers has improved outcomes among patients with severe asthma in developed countries [5]. However, the integration of immunological interventions a mentioned above in asthma standard treatment guidelines of developing countries remains limited or unknown. This may compromise the quality of asthma care received by the population and lead to sub-optimal outcomes particularly among patients with severe asthma in both children and adults. Consequently, the current review aims to describe the immunological progress in the diagnosis and management of asthma in order to provide policy guidance for integration in asthma care in sub-Sahara Africa.

## Methodology

**Design, search strategy and inclusion criteria:** A systematic review was conducted between January 2014 and March 2019 that reported progress in diagnosis and/or treatment asthma. The search strategy including key terms that is asthma, management and immunology was applied in search engines. Boolean operators such as AND, OR, * and wt. were used alongside the synonyms for the key terms to focus the search. The databases included Mendeley, Medline, PubMed, and EMBASE, Google scholar, Cochrane library, Scopus and reference lists of retrieved articles. Two reviewers (i.e. AK and DK) identified articles that were relevant to the study objectives and their abstracts and full papers reviewed for inclusion. The reviewers independently included the studies based on the eligibility criteria and methodological quality suggested by Cochrane. The systematic identification, appraisal, synthesis and aggregation of all relevant studies on asthma and immunology reduced bias of the review. Other aspects of the ethology of asthma e.g. Genetics, epigenetic modifications and the contribution of the environment were excluded from the review.

## Objectives of the Review

1. Delineate the roles of the innate and adaptive immune systems and components in the immune-pathogenesis of asthma
2. Outline the rationale of biomarkers, phenotyping and biologic agents in the treatment of asthma i.e. Precision tailored asthma medicine.
3. Describe distinct clinical phenotypes and endotypes of asthma that suggest differences in pathophysiologic mechanisms using modelling approaches.

## Data analysis

All data was analyzed qualitatively through thematic analysis. The main themes described immunology, immune cells and mucosal immunology and treatment of asthma both in adults and children.

## Ethical approval

Ethical approval was waived as the study used published secondary data (i.e. publications). In addition, there was no need to include any and/or patient specific identifiers such as names in this study.

## Results

### Immuno-pathogenesis of asthma

Asthma is a complex clinical heterogeneous syndrome disease characterized by inflammation and airway abnormalities. Multiple phenotypes, with varying underlying biology, are now recognized [5]. Although there are different paradigms for establishing relevant phenotypes, asthma can broadly be separated into two categories: eosinophilic (T-helper 2 [Th2]) and non-eosinophilic (non-Th2).

Each category has a different underlying immuno-pathogenesis, and recently approved medications for asthma all target the eosinophilic/Th2 type of disease. The inflammatory response in the airways of patients with asthma involves an orchestrated interplay of the respiratory epithelium, innate immune system, and adaptive immunity that initiates and drives a chronic inflammatory response.

For patients with eosinophilic/Th2 asthma, the disease is typically exacerbated by inhaled "triggers". Triggers include allergens, pollutants and infections that make contact with the airway epithelium and induce an inflammatory cascade. This cascade includes multiple cytokines, or cellular messengers, that help coordinate an immune response to a given trigger. Cytokines, such as interleukins (ILs), interact with cells and immunoglobulins (Igs) to activate eosinophils, mast cells, and leukotrienes, and stimulate mucus and histamine release. The end result for the patient is bronchoconstriction; chest congestion; and cough, dyspnea, and wheezing.

Recently developed monoclonal antibodies, also referred to as "biologics," target different levels of the eosinophilic/Th2 asthmatic response.

Omalizumab blocks the interaction of IgE with its receptor and is approved by the US Food and Drug Administration (FDA) for the treatment of asthma

Mepolizumab and reslizumab are IL-5 antagonists and benralizumab is an IL-5 receptor antagonist-all are also FDA-approved for the treatment of asthma.

Dupilumab acts on the IL-4 receptor and affects IL-4 and IL-13; and recent studies show benefit, it is now approved by the FDA. These five biological agents have fundamentally changed the treatment severe asthma care and treatment.

Phenotypes and endo-types classification of Asthma has largely been achieved through cluster analysis of asthmatic cohorts using software of machine learning or "big data" [5] and micro-array analysis. This technology of machine learning and microarray analysis is still unavailable in most parts of Sub-Saharan Africa including Southern Africa where studies concerning asthma have involved use of questionnaires mainly but not physician diagnosed asthma [6,7].One such study [6] did involve adolescents age 13 thru 14 years of age [6].

Physician Diagnosed Asthma (PDA)" is a concept that is widely used as a specific characteristic to describe, and/or classify patients in various clinical and epidemiologic studies [8,9].

Asthma is characterized by a response from both immune and epithelial cells. These cells differ in components, structure and function. The categories of cells involved in the immune response to asthma and their function, in summary includes:

(a) Neutrophils, phagocytes, macrophages, eosinophils, basophils, mast cells, innate lymphoid cells, dendritic cells through pattern recognition by these cells via IL-25, IL33, Thymic Stromal Lymphopoietin and Clara (CC16 cells).

(b) T and B-lymphocytes, Treg cells.

(c) As well as the role of the airway epithelium in asthma immunopathogenesis [10]. Epithelial damage is a characteristic feature of asthma. The epithelium is not merely a passive barrier but can generate a range of mediators that play a role in the inflammatory and remodeling responses that occur in the lungs in asthma.

## The immune response

The immune response (i.e. when lymphocytes identify the antigenic molecule as foreign and induce the formation of antibodies and lymphocytes capable of reacting with it and rendering it harmless) is a common characteristic of asthma. In the immune response, all immune cells originate from the hematopoietic stem cells in the bone marrow. The T lymphocytes then undergo maturation in the thymus. The thymus and bone marrow are known as primary lymphoid tissues. Secondary lymphoid tissues that include lymph nodes, spleen and mucosa-associated lymphoid tissues (MALT) are sites for adaptive immune responses. MALT are an important mucosal immune defense system of the gastrointestinal tract and airways. Lymph nodes positioned along the lymph vessels monitor the lymph for infection. The spleen essentially serves as a 'lymph node' for the blood.

## Components of Innate Immunity and their role in innate immune responses

The cellular innate response mainly consists of phagocytes, specifically neutrophils and macrophages as well as natural killer cells (NK). The phagocytic response involves, the recognition of microorganisms occurs via characteristic pathogen-associated molecular patterns (PAMPs) on surfaces of microorganisms, and innate receptors known as pattern-recognition receptors (PRRs) for example the Toll-like receptors (TLRs). On the other hand, the NK cellular response targets intracellular infections of cells by viruses. The innate immune system relies on changing pattern recognition of receptors to detect common pathogens or the damage they cause; to the adaptive immune system. It relies on a range of antigen receptors to recognize structures that are specific to individual pathogens. Hence, the adaptive immunity has greater sensitivity and specificity. The clonal expansion of antigen-reactive lymphocytes also confers the property of immunologic memory to lymphocytes.

The hematopoietic stem cells has evolved since their discovery in 1961. Hematopoietic cells have long-term or short-term regeneration capacities with either, committed multipotent, oligo-potent, or unipotent progenitors.

Myelopoiesis is defined as the regulated formation of myeloid leukocytes (i.e. eosinophilic granulocytes, basophilic granulocytes, neutrophilic granulocytes, and monocytes and megakaryocytes as well as mast cells and myeloblasts. The latter leading to granulocytes and monocytes, macrophages, and dendritic cells of the innate immune system. Similarly, lymphopoiesis is the generation of lymphocytes The myeloid lineage comprises most of the cells of the innate immune system [11].

## Cells involved in the immune response to asthma

### Granulocytes

These include basophils, eosinophils and neutrophils also known as polymorphonuclear cells. Neutrophils are the most abundant white blood cells (55 - 65%) that are primarily responsible for maintaining host defenses against invading bacteria or foreign matter. Basophils are the least numerous of the WBC accounting for only 0.3 to 0.5% and contain heparin, histamine and other mediators of inflammation. Eosinophils account for 1 - 5% of WBCs and increase in number with allergic diseases such as Asthma [12,13].

### Phagocytes

Phagocytic cells are a part of the innate immune system and consist of poly-morphonuclear cells, monocytes-macrophages and eosinophils. Neutrophils and monocytes circulate in the bloodstream and are recruited to sites of infection by the process of extravasation. Receptors on the phagocyte interact with ligands on vascular endothelium, and the cells attach, arrest, and move from the circulation to the diseased tissue/lungs**.** Four types of immune cells (i.e. neutrophils, monocytes, macrophages and eosinophils) are specialized for phagocytosis. Neutrophils and monocytes are roving phagocytes. Macrophages are larger, tissue resident phagocytes. The processing by phagocytosis is important for generating specific immune responses. Among the granulocytes, neutrophils and eosinophils are phagocytic but not basophils [14].

### Macrophages

Are specialized to detect, phagocytose and destroy bacteria and other harmful organisms derived from bone marrow and occur in most tissues, including lymphoid tissues are critical for the initiation of the immune response. They derive their name from the long membranous extensions that cover the cell like that of nerves.

### Dendritic cells

Dendritic cells capture antigens e.g. pollen animal fur and process these antigens' and then present them to naïve T cells, initiating the adaptive immune response. The first stage of an immune response to any antigen is the processing and presentation of that antigen-by-antigen presenting cells (APCs) such as dendritic cells.

### Mast cells

Are a large granule-rich cell found in connective tissue the body, most abundantly in the submucosal tissues and the dermis. The granules store bioactive molecules including the vasoactive amine, which are released on mast cell-activated and are involved in the pathogenesis of bronchoconstriction in asthmatics airways [15].

### Eosinophils

Stain with eosin and are effector cells in asthma and produce cytokines e.g. IL-5. In the airway of asthmatic patients, eosinophil derived mediators of inflammation including eosinophil derived neuro-toxin (EDN), major basic protein (MBP) and lysophopholipase (LPL) are toxic to the respiratory epithelium contributing to the immune-pathogenesis of asthma in both children and adults [16-18].

### Basophils

Stain with basic dyes and are however non-phagocytic granulocytes. In response to binding of circulating antibodies, basophils release their contents including histamine that causes smooth muscle contraction in asthmatic airways as well as increasing blood permeability, these accounts for the edema of the airways in asthma and inflammation [19,20]. Basophils and mast cells release mediators of immediate hypersensitivity such as histamine.

### Pattern recognition receptors (PRRS) of the innate immune system

The innate immune system distinguishes microbes by their molecular components that are not made by the host. These pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors (PRRs). Compelling experimental evidence has demonstrated that asthma does not exclusively depend on Th2 adaptive immune responses, and it is increasingly seen as a disease that has a strong innate immune component. Different innate immune system cells in the lung such as epithelial cells, DCs, other airway cells, neutrophils, eosinophils, NK cells and NKT cells as well as ILC2 also significantly contribute to the initiation and maintenance of allergic asthma.

The innate immune system cells express a wide range of pattern recognition receptors (PRRs) that allow them to recognize molecular patterns released from pathogens (pathogen-associated molecular patterns, PAMPs) or from damaged tissues (damage-associated molecular patterns, DAMPs). Innate immune system cells respond to environmental insults such as cigarette smoke that may directly damage respiratory tissues, activating damage PRRs, or to respiratory viruses activating Toll-like receptor (TLR)3, TLR7 or TLR8, which leads to inflammation, and synergize to significantly exacerbate lung inflammation. In the same way, other PRRs including C-type lectin receptors, scavenger receptors or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) could also contribute to enhance inflammation after exposure to protease-containing allergens, pathogens or pollution.

Innate immune defenses are highly efficient and include homeostatic mechanisms that downregulate inflammation to optimize the health of the host. Like antimicrobial immunity, allergen recognition and uptake, allergic sensitization, inflammation, and disease originate in the innate immune system.

The PRRS are receptors of the innate immune system that recognize common molecular patterns on pathogen surfaces called pathogen-associated molecular patterns (PAMPS), structures that are conserved in broad classes of pathogens for their functional importance. Many of these receptors reside at the plasma membrane. They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils and epithelial cells [21-24].

**C-type lectins:** A group of PRR receptors recognizes certain sugar units that are typically located at the terminal position of carbohydrate chains on pathogen surfaces.

**Toll-like receptor (TLR):** The best-characterized signaling PRR families is the evolutionary conserved toll-like receptor (TLR) system in mammals, named after a homologous receptor system used by the Drosophila fruit fly for protection from infection.

**Natural killer cells:** An innate lymphoid cell (ILC) that is important in innate immunity to viruses and other intracellular pathogens, and in antibody-dependent cell mediated cytotoxicity (ADCC). They do not express antigen receptors and are considered part of the innate immune system, despite being lymphoid cell [25].

**NKT cells:** Another type of cell in the lymphoid lineage that shares features with both conventional T lymphocytes and NK cells. Like T cells, NKT cells have T-cell receptors (TCRs) and some express CD4. Unlike most T cells, however the TCRs of NKT cells are not very diverse and recognize specific lipids and glycolipids presented by a molecule related to the Major Histocompatibility Complex (MHC) proteins called CD1.

Like their innate immune counterparts, NK cells, NKT cells have antibody receptors.

NKT cells are considered as a cell subset belonging to the innate immune system with the capacity to amplify adaptive immune responses in asthma.

### Innate lymphoid cells

Additional lineages of cells related to NK cells have been identified. Collectively, these cells are called innate lymphoid cells.

**Innate lymphoid cells (ILC):** Are cells of the innate defense system that are similar to B or T lymphocytes under the microscope, but do not express B nor T cells receptors. The ILCs play a role as regulators of innate immunity, inflammation, and tissue repair at the barrier surfaces. They are a lymphoid subclass characterized by the lack of either B- or T-cell receptors but retain cytotoxic and immunomodulatory capacity [26].

The ILCs are classified into three groups. However unlike T cells and B cells, ILCs do not have antigen receptors. They respond to innate factors released by the bronchial epithelium, such as cytokines and alarmins, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) [27-29]. ILCs produce multiple pro-inflammatory and immune-regulatory cytokines.

### CC16CLUB cells/Clara cells

Of recent Clara cells (CC16) have re-emerged in the immuno-pathogenesis of Asthma. CC16 is suggested to be a protective mediator in the airway in-inflammatory processes. Severe refractory asthma (SRA) is characterized by an amplified inflammatory and a re-modelling process. Clara cell secretory protein (CC 16) is an anti-inflammatory protein associated with Th2 response modulation (regulation).

**IL-25, IL33 and TLSP:** Are epithelial derived cytokines and have been identified as having an important role in asthma pathogenesis. These cytokines have been described as epithelial-derived alarmins that activate and potentiate the innate and humoral arms of the immune system in the presence of actual or perceived damage. TSLP is increased in asthmatic airways and mast cells, and in the lungs is produced mainly by airway epithelial cells. In addition, these three cytokines can generate a Th2 cytokine profile independent of the adaptive immune system. TSLP and IL-33 directly induce the full repertoire of Th2 cytokine secretion from mast cells. Similarly, IL-25, TSLP and IL-33 act on type 2 innate lymphoid cells (ILC2) to drive their more restricted secretion of IL-5 and IL-13.

### Adaptive immunity and asthma pathogenesis:

Adaptive immune responses depend on activation of naïve CD4+ T cells and differentiation into effector cells. Multiple signals coordinate differentiation into specific CD4+ T effector cell subsets: helper T (Th) cells (Th1, Th2, and Th17) and regulatory T (Treg) cells. "CD4+ Th2 cells are critical mediators of inflammation in asthma".

Treg cells may help to prevent the development of asthma.

**T cells:** The T cell responses to antigens consist of a combination of pro-inflammatory (effector) and anti-inflammatory (regulatory) cells. Lymphocytes differentiate into separate lineages. The B-lymphocytes secrete antibodies [11]. Although both originate in the bone marrow, T cells mature in the thymus, whilst B cells mature in the bone marrow. Adaptive immunity is mediated by lymphocytes stimulated by microbial antigens, requires clonal expansion and differentiation of the lymphocytes before it is effective. The T lymphocytes operate in a supervising role to mediate cellular and humoral responses. Antigen presentation describes a vital immune process, which is essential for T cell immune response triggering immunity. B and T lymphocytes produce and express specific receptors for antigens. Collectively, the functions of the T and B cells encompass an entity called the adaptive immune system [24]. T-helper lymphocytes conventionally are TH1 and TH2 cells. TH1 cells produce cytokines that down regulate the atopic response. In those who are genetically susceptible to developing asthma, antigen presentation to T-helper cells leads to a TH2 response.pro-inflammatory cytokines and up-regulation of airway inflammation of asthma by enhancing Immunoglobulin E (IgE) synthesis, eosinophils and mast cell activation/function.

### TREG cells

### Regulatory T cells and immune tolerance

TREG cells comprise a group of different T cell subsets with suppressive capacity that are essential for the induction of immune tolerance. TREG cells can be broadly divided into two main groups:

(1) The thymus-derived naturally occurring CD4+CD25+ forkhead box protein 3 (FOXP3)+ TREG cells, also called natural TREG (nTREG) cells, and

(2) The inducible TREG (iTREG) cells. nTREG cells constitutively express high levels of the alpha chain of the IL-2 receptor (CD25) and the suppressor costimulatory molecules CTLA4 and PD1 [30,31].

Regulatory T cells (Tregs) are a class of CD4+ T cells (T-helper cells), which do not directly kill infected ells but activate cytotoxic cells to attack infected cells or stimulate B cells to secrete antibodies. regs play a key role in asthma but also aid in the maintenance of peripheral tolerance, modulation of immune responses, and prevention of autoimmune diseases [30-32]. Tregs are regarded as essential for controlling chronic inflammatory disease and modulating allergic inflammation.

### The respiratory airway cells

Allergic sensitization to inhaled antigens is common but poorly understood. Although lung epithelial cells were initially merely regarded as a passive barrier impeding allergen penetrance, we now realize that they recognize allergens through expression of pattern recognition receptors and mount an innate immune response driven by activation of nuclear factor kB. On allergen recognition, epithelial

cells release cytokines, such as IL-1, IL-25, IL-33, thymic stromal lymphopoietin, and GM-CSF, and endogenous danger signals, such as high-mobility group box 1,uric acid, and ATP, that activate the dendritic cell network and other innate immune cells, such as basophils and type 2 innate lymphoid cells [33,34].

The epithelium contains ciliated columnar cells, basal cells, goblet cells and neuroendocrine cells amongst others. Some of these cells but not all are involved in the immune-pathogenesis of asthma e.g. Goblet cells produce mucous. Increased number of goblet cells (Goblet cell hyperplasia) is part of airway remodeling in Asthma. Mucus is a complex solution of lipids and proteins that lines the airway lumen. In respiratory conditions like asthma that are associated with mucus hypersecretion, mucus ceases to be protective and instead contributes to the immunopathology of asthma. The function of mucous is to trap inhaled particles/allergen and the interaction with the tips of beating cilia, remove particles/allergen from the airways, a process termed muco-ciliary clearance [35]. Other cells of the epithelium e.g. neuroendocrine cells are not directly involved in the immune-pathogenesis of Asthma. Neuroendocrine cells are small round cells with dark staining nucleus and clear cytoplasm. These cells contain characteristic neuroendocrine granules and secrete hormones and active peptides including serotonin. Smooth muscle, lymphoid tissue and sero-mucous glands are present in the wall of the bronchi. In the last few years, several cell- and molecular-biological characteristics of these cell types are investigated and their importance to physiological and pathological processes has been clarified. The products of secretory cell types are essential for the muco-ciliary clearance and thus play an important part in host- defense. In many diseases, such as asthma the structure and function of these cells are altered in a characteristic way. As a consequence of the events described above. the wall of the airway in asthma becomes thickened by edema, cellular infiltration, increased smooth muscle mass and glands, i.e. remodeling of the airways occurs, the bronchial thermoplasty targets this phenomenon. Structural changes in the epithelium of the airway, termed "airway remodeling," consists of airway wall thickening, epithelial hypertrophy and mucous metaplasia, sub-epithelial fibrosis, myo-fibroblast hyperplasia, and smooth muscle cell hyperplasia and hypertrophy. Airway remodeling is thought to represent a response to ongoing tissue injury caused by infectious agents, allergens, or inhaled particulates and by the host responses to these stimuli [35]. Viral respiratory tract infections are a major trigger for asthma exacerbations in a large number of patients, which explains the seasonal increase in asthma exacerbations during the winter months. Other common triggers for asthma exacerbations are exercise, weather changes, and exposure to tobacco or other smoke, air pollution and smog, cold or hot air, strong perfumes, or other irritants. Children who are atopic are especially susceptible to environmental allergens, and a small subgroup of children have asthma that is triggered by drugs such as aspirin (approximately 5%) or b-adrenergic blocking agents. These drugs should therefore be used cautiously, especially in children with severe and poorly controlled asthma.

## Pathogenesis/emerging asthma phenotypes and endotypes

While asthma is considered an inflammatory disorder of the conducting airways, it is becoming increasingly apparent that the disease is heterogeneous with respect to immunopathology, clinical phenotypes, response to therapies, and natural history. Once considered purely an allergic disorder dominated by Th2-type lymphocytes, IgE, mast cells, eosinophils, macrophages, and cytokines, the disease also involves local epithelial, mesenchymal, vascular and neurologic events that are involved in directing the Th2 phenotype to the lung and through aberrant injury-repair mechanisms to re-modelling of the airway wall [36].

## Eosinophilic versus non-eosinophilic asthma

Asthma is described as a` heterogeneous' disease with chronic inflammation of the airways in association with structural changes of the airway wall involving the participation of both infiltrating and resident cells. A number of underlying mechanisms have been proposed for the asthmatic inflammatory response.

Of these, the CD4 T-helper cell type 2 (Th2)-mediated pathway is characterized by eosinophilic inflammation and elevated levels of type 2 cytokines, such as IL-4, IL-5 and IL-13 within the airway and the majority of patients with the so-called Th2high endo-type have an allergic phenotype [37].

### The sentinel role of the airway epithelium in asthma pathogenesis

The adoption of the concept that asthma is primarily a disease most frequently associated with elaboration of T-helper 2 (Th2)-type inflammation has led to the widely held concept that its origins, exacerbation, and persistence are allergen driven. Taking aside the asthma that is expressed in non-allergic individuals leaves the great proportion of asthma that is associated with allergy (or atopy) and that often has its onset in early childhood. Evidence is presented that asthma is primarily an epithelial disorder and that its origin as well as its clinical manifestations have more to do with altered epithelial physical and functional barrier properties than being purely linked to allergic pathways [38]. The ultimate goal of current research is to identify biomarkers that define subtypes of asthma that respond to specific therapies – often called personalized or precision medicine.

The airway epithelium has traditionally been considered an inert barrier, but it has become accepted as a dynamic structure playing a pivotal role in controlling many airway functions and intricately involved in airway homeostasis. Data from the study of tissue obtained from children and adults indicate that the airway epithelium of asthmatics is structurally and functionally abnormal, which has a significant impact on airway inflammation, immunity, and remodelling [35]. The epithelium plays an important role as a physical and immune barrier. Airway remodelling is a summary term that describes structural changes in the airway in asthma. The pathology includes changes throughout the airway wall, including the epithelium. The epithelium regulates airway homeostasis through the production of a multitude of cytokines, chemokines, lipid mediators, and growth factors. Epithelial cells bridge the innate and adaptive immune responses by translating environmental exposures into disease phenotypes [35].

### The evolving definition of asthma goals pharmacotherapy

In I960s (i.e. the bronchodilator era), the main stay and concept of management of asthma included the episodic treatment of symptoms. In1980s, i.e. the inflammation era where Inhaled corticosteroids (ICS) where the mainstay of asthma treatment. Recently, a biologic phase for management of asthma is being advanced as the most appropriated for severe states of the disease.

### Quality asthma care

Quality asthma care involves not only initial diagnosis and treatment to achieve asthma control, but also long-term, regular follow-up care to maintain control. Most guidelines emphasize the importance of matching pharmacotherapy to severity of disease, which requires periodic reassessment by patients and clinicians. The goals of therapy are to prevent symptoms, minimize need for rescue medications, maintain lung function and activity, and reduce risk for exacerbations. International guidelines consistently describe the goals of asthma treatment to include the control of patients' current symptoms and the prevention of recurrent exacerbations.

**Definition of an asthma exacerbation:** International guidelines consistently describe the goals of asthma treatment to include the control of patients' current symptoms and the prevention of recurrent exacerbations. Several definitions of an asthma exacerbation and exacerbation severity have been put forth by various groups, including the Global Initiative for Asthma (GINA), the NHLBI/National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3), and the ATS/ERS Statement.

The GINA guidelines define "acute exacerbations" (asthma attacks or acute asthma) as "episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms, accompanied by decreases in expiratory airflow that can be quantified by measurement of lung function" (p 69). These guidelines also define exacerbations as acute and severe loss of control that requires urgent treatment. The GINA guidelines refer to the severity of exacerbations but do not define exact criteria by which to distinguish severity levels.

Four components/aspects are addressed in the GINA definition of exacerbations i.e. as the foundation for assessing asthma control in adults, adolescents, and children aged 6 to 11 years, the Global Initiative for Asthma, or 'GINA,' recommends asking patients about 4 specific aspects of their symptoms over the preceding 4 weeks:

(1) Whether they have experienced daytime symptoms more than twice a week;

(2) Whether they have woken during the night due to asthma symptoms;

(3) Whether they have used their rescue inhaler for the relief of symptoms more than twice a week, not including use prior to exercise; and

(4) Whether they have had any activity limitation caused by their asthma symptoms.

### Interpretation of asthma exacerbations

If none of these 4 criteria apply, the patient's asthma is well controlled. If 1 or 2 of the criteria are met, they are using their inhaler as prescribed, and there is no environmental explanation for their symptoms, their asthma can be considered partly controlled and if 3 or 4 of the criteria are met, their asthma is uncontrolled.

### Severe asthma

Asthma is a heterogeneous condition. Its natural history includes acute episodic deterioration (exacerbations) against a background of chronic persistent inflammation and/or structural changes that may be associated with persistent symptoms and reduced lung function. Trigger factor exposure combines with the underlying phenotype, the degree of hyper-responsiveness and of airflow obstruction, and the severity of airway inflammation to cause wide variability in the manifestations of asthma in individual patients. When the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high dose corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled "despite this therapy. Using GINA guidelines this occurs at Step four (4) level of therapy.

**The current guidelines emphasize four important components of asthma care, as follows:** *(*i) Assessment and monitoring. (ii) Education. (iii)Control of environmental factors and comorbid conditions. (iv) pharmacologic treatment. NB. Guidelines emphasize the importance of matching pharmacotherapy to severity of disease, which requires periodic reassessment by patients and clinicians. The goals of therapy are to prevent symptoms, minimize need for rescue medications, maintain lung function and activity, and reduce risk for exacerbations.

### Pharmacological management of asthma

- The SAMA, i.e. Short Acting Muscarinic Antagonists e.g. Ipratropium.
- The LAMA, i.e. Long-acting muscarinic antagonists, have been shown to reduce exacerbations of chronic obstructive pulmonary disease (COPD) and are now being considered for patients with uncontrolled asthma as add-on treatment e.g. Tiotropium.

Five Biologicals Are Food and Drug Administration (FDA) U.S.A approved (October 2018) in the U.S.A. These and their brief summary of mechanism of action: Omalizumab-Anti IgE, Mepolizumab-Anti IL5, Resiluzumab-Anti-IL-5, Benralizumab-Anti IL-5 receptor and Dupilumab-Anti-IL4a subunit of IL4 and IL13.

The dosing tables for Omalizumab are available and good for children. The dosage depends in IgE levels. The patient's pretreatment serum total IgE level (IU/mL) and body weight (lb or kg) are used to determine doses (mg) and dosing frequency.

Omalizumab is dosed every 2 or 4 weeks. Of these, only resilizumab, an anti-IL-5 antibody, is not approved in adolescents. Patients must be 18 years of age or older to receive resilizumab and must have eosinophil levels > 400 cells/μL. Mepolizumab, a second anti-IL-5 antibody, may be used in patients over 12 years of age who have an eosinophilic phenotype. Benralizumab (Fasenra®), also an anti-IL-5 agent, reduces exacerbations at about the same amount as mepolizumab and has been reported to enable a 75% reduction in corticosteroid use. Dupilumab inhibits IL-4 and IL-13 and shows evidence for improving severe asthma that resists conventional management.

## Current and emerging therapies in severe asthma (TH2 high, TH2 low)

For the majority of patients, current treatment options offer good control of their disease, however 10 - 20% of patients(Adults) and 5%%( children) do not achieve control with current gold standards of care. Severe asthma in children is characterized by sustained symptoms despite treatment with high doses of ICS or oral corticosteroids and represents approximately 5% of childhood asthma cases [40,41]. Although this does not sound like that many, they account for 60% of all asthma costs.

These costs rival those for very resource-intensive diseases like type 2 diabetes, chronic obstructive pulmonary disease, and cerebrovascular accidents.

Although the majority of children with asthma respond well to standard therapy, a significant proportion [still have problematic, severe disease that is not controlled with conventional management [41]. A birth cohort identified 4.5% of the asthmatic children with ''severe asthma'', whereas others found that 39 - 55% of children with problematic severe asthma had ''difficult to treat'' asthma [42-44].

## The role of the airway epithelium

Investigations regarding the airway epithelium have led to many advances over the past few decades, but new developments in genetics and stem cell/progenitor cell biology have opened the door to understanding how the airway epithelium is developed and maintained and its role in asthma immunopathogenesis [45,46]. An abnormal immune response to environmental agents is generally thought to be responsible for causing chronic respiratory diseases, such as asthma. There is increasing evidence that the response of the innate immune system is crucial for the development of this type of airway disease. Airway epithelial cells and innate immune cells represent key components of the immunopathogenesis of chronic airway disease and are emerging targets for new therapies. Asthma is a common heterogeneous disease with a complex pathophysiology. Current therapies based on inhaled corticosteroids and long acting β2 agonists are effective in controlling asthma in most, but not all patients, with a few patients falling into the severe asthma category. Airway inflammation is one of the pathophysiological characteristics of asthma, which is mediated through infiltration of inflammatory cells, including mast cells, and eosinophilic and neutrophilic granulocytes in the airway wall. This cell infiltration subsequently leads to bronchial hyper responsiveness (BHR) and in the case of chronic inflammation, persistent changes of the airways, i.e. airway remodeling [47-52].

## Bronchial thermoplasty

This technique uses radio frequency energy to attenuate airway smooth muscle mass, thereby reducing bronchoconstriction and airway remodelling. The procedure was approved for clinical use in 2010 for adult patients with severe persistent asthma not controlled with ICS/LABA.

Modality for treating severe asthma in adults, because of structural changes that have risen (Airway remodeling). Involves application of heat. Catheter introduced (Attached to an electrical unit)-converted to heat-applied into airway wall.

## Asthma patient education

A collaborative and trusting relationship between the family and the medical professionals is critical for successful long-term management of the disease. Families that have a child with asthma need to learn how to correctly give daily maintenance medication and how to detect and respond appropriately to fluctuations in asthma control, knowing when to seek professional help and when to go to the emergency department Asthma action plans provide a way to involve patients directly in self-management by providing clear, written instructions of the agreed-upon treatment plan for at-home use. The plans are essential for self-monitoring, enabling patients to assess their level of asthma with asthma will benefit from written asthma action plans developed in partnership with the patient

- Function and appropriate use of medication
- Pathophysiology of asthma
- Issues in the prevention and treatment of symptoms.

## Conclusions

### Re-defining asthma the evolving definition of asthma

Asthma is not only variable within individuals but also highly heterogeneous (diverse/varied) across the population. Asthma should nor longer be used as a disease entity without recognizing underlying treatable traits to be assessed, monitored, and managed individually, taking into account treatable traits to be assessed, monitored and managed individually, taking into account comorbidities and lifestyle and environmental factors into account. Recent research has focused on identifying features that differentiate these forms of asthma, as well as targets for individualizing therapy – in other words, biomarkers. It is increasingly clear that asthma is a complex disease/syndrome made up of number of disease variants with different underlying patho-physiologies. There is importance and clinical relevance of impairment and risk as components of severity and asthma control. We are moving away from clinical to molecular approaches in the diagnosis of asthma. There have been substantial advances in the understanding of asthma genetics, airway biology, and immune cell signaling. These advances have led to the development of small molecule therapeutics and biologic agents that improve asthma care Biologic agents for asthma treatment provide targeted therapy for patients with specific asthma phenotypes. Ongoing clinical trials are evaluating these agents to help broaden the current arsenal of asthma treatment options.

### Recommendations

Between 10 - 20% of adult patients and 2 to 5% of children, do not achieve control with current gold standards of care. As we have developed a better understanding of the inflammatory markers involved in the disease and the various phenotypes and endo types of asthmatic patients, biologic agents, like the ones described in this review, should be made available for patients with severe asthma, including children ,adolescents and adults that are poorly controlled in Sub-Saharan Africa. These agents have been shown to be cost effective. This knowledge should be considered for translation into public health policy as well as clinical practice.

### Acknowledgments

Professor Peter Nyarango, Dean, School of Medicine, Hage Geingob Campus, University of Namibia, Windhoek, Namibia.

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**Volume 8 Issue 9 September 2019**