

Contemporary diagnosis and management of childhood asthma

Andrew Kiboneka *

Department of Pediatrics, Case Hospital, Kampala, Uganda.

World Journal of Advanced Research and Reviews, 2021, 10(01), 373–380

Publication history: Received on 17 March 2021; revised on 25 April 2021; accepted on 27 April 2021

Article DOI: <https://doi.org/10.30574/wjarr.2021.10.1.0173>

Abstract

Asthma is a chronic heterogeneous inflammatory disorder/syndrome of the airways that affects more than 300 Million people worldwide. Asthma often starts in childhood (Allergic Asthma phenotype). Co morbidities often trigger asthma exacerbations. It's often difficult to diagnose asthma in young children. Objective tests of lung function aid in the diagnosis of asthma in children > six years of age. Asthma has phenotypes and endotypes. Biomarkers Ex. Fractional excretion of Nitric Oxide aid in the diagnosis of severe asthma in children and adults.

Management of Severe Asthma has undergone a revolution. Asthma is responsible for considerable global morbidity and health-care costs. Substantial progress was made against key outcomes such as hospital admissions with asthma and mortality in the 1990s and early 2000s, but little improvement has been observed in the past 10 years, despite escalating treatment costs.

Keywords: Childhood Asthma; Contemporary diagnosis and management

1. Introduction

Childhood asthma (pediatric asthma) is the most common serious chronic disease in children and adolescents; yet is often difficult to diagnose. [1]. Many guidelines exist that aid in the definition, diagnosis and management of childhood asthma. Notable is the Global initiative on Asthma (GINA), the Global Strategy for Asthma Management and Prevention, the American Thoracic society (ATS) and the European Respiratory Society. (ERS). "Asthma is a heterogeneous syndrome, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Symptoms are often reversible but not always. Sub endothelial fibrosis and changes in the airway epithelium can occur. [2]. In children the causes and differential diagnosis of asthma are diverse and not all that wheezes is asthma. In particular, asthma is difficult to diagnose in infants.

2. Material and methods

The search strategy included all articles on PuB Med Search Engine, published in English between June 2020 and February 2021. 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.

*Corresponding author: Andrew Kiboneka
Department of Pediatrics, Case Hospital, Kampala, Uganda.

3. Results

Asthma is a serious global health problem affecting all age groups, with global prevalence ranging from 1% to 21% in adults and children [3,4], and with up to 20% of children aged 6–7 years experiencing severe wheezing episodes within a year [5]. Asthma may affect as many as 334 Million People worldwide. In Sub Saharan Africa, particularly Southern Africa, the burden of Asthma in Children may be underestimated as there is paucity of literature pertaining to childhood asthma in Botswana, Namibia, Swaziland and Lesotho. Most of the work concerning childhood asthma in these countries has been carried out in the Republic of South Africa. [6,7].

4. Discussion

4.1. Immunopathogenesis of asthma (cells, molecules and the airway epithelium in childhood asthma)

Inflammation, immune cells and airway epithelial changes characterize the syndrome of Childhood asthma. Asthma is a chronic respiratory disorder characterized by infiltration of many immune cells in the airway epithelium. The role of inflammation in childhood asthma is well known, characterized by numerous cells including mast cells, eosinophils, lymphocytes, innate lymphoid cells etc). Development of distinct childhood asthma phenotypes, are currently included under the term the asthma syndrome.

Epithelial cell–Dendritic cells (DC) crosstalk is crucial for asthma development.

Epithelium-derived cytokines contribute to ILC2 responses

Basophils have no role in Th2 sensitization to HDM, but contribute to the effector phase.

Respiratory epithelium, or airway epithelium, is a type of ciliated columnar epithelium found lining most of the respiratory tract as respiratory mucosa, where it serves to moisten and protect the airways. Increasing evidence suggests that airway wall remodeling is initiated early in life by epigenetic events that lead to cell type specific pathologies and modulate the interaction between epithelial and sub-epithelial cells.

Asthma is associated with immune system activation, airway hyper responsiveness (AHR), epithelial cell activation, mucus overproduction and airway remodeling. Both innate and adaptive immunity play roles in immunologic mechanisms of asthma.

Type 2 asthma with eosinophilia is a common phenotype in asthma. [8]. Allergic asthma is the most common form of asthma. In allergic asthma, the body initiates an immune response to an allergen such as pet dander, dust-mites, mold or pollen that results in IgE antibodies. This process is commonly referred to as allergic sensitization. [8]

Type 2-immunity represents the typical adaptive response to allergen exposure in atopic individuals. It mainly involves Th2 cells and immunoglobulin E, as the main orchestrators of type 2-inflammation. The immune-histopathologic features of asthma include epithelial injury and infiltration of inflammatory cells, consisting of eosinophils, lymphocytes, mast cells, and phagocytes. Inflammatory mediators released by these cells are the effectors of chronic inflammation. The pathophysiology of asthma is complex and involves airway inflammation, intermittent airflow obstruction, and bronchial hyper responsiveness. . Airway hyper responsiveness or bronchial hyper reactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli.

The innate immune system harnesses receptors that recognize conserved pathogen patterns and alongside the more specific recognition systems and memory of adaptive immunity, their interplay is evidenced by respective roles during generation and regulation of immune responses. The concepts underlying asthma pathogenesis have dramatically evolved over the past 30 years, and understanding of this complex disease continues to increase.[9]

It is now clear that asthma is not a single disease, but rather a syndrome that can be caused by multiple biologic mechanisms. 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 involving many immune cells. The cells of the immune system can be categorized as lymphocytes (T-cells, B-cells and NK cells), neutrophils, and monocytes/macrophages. These are all types of white blood cells. The major proteins of the immune system are predominantly signaling proteins (often called cytokines), antibodies, and complement proteins. Convention has led to a bipartite classification of the adaptive immune system,

wherein Th1 cells mediate delayed-type hypersensitivity reactions and selectively produce IL-2 and IFN- γ , and Th2 cells promote B cell-dependent humoral immunity and produce IL-4, IL-5, and IL-13[9]

In the case of asthma, the “Th2 hypothesis” proposes that an upregulated Th2 and a downregulated Th1 response drive the development of disease.

More recently a very exciting recent development was the discovery of innate lymphoid cells (ILCs) as key players in the pathogenesis of asthma. Type 2 innate lymphoid cells (ILC2s) were first characterized in 2010 as an interleukin 13 (IL-13)-producing non-B/non-T innate effector cell type crucial in type 2 immune responses, such as helminth infection.

ILCs do not express antigen receptors but react promptly to “danger signals” from inflamed tissue and produce an array of cytokines that direct the ensuing immune response. For several decades, asthma was thought of as an immunologic disease mediated by TH2 cells and adaptive immunity. Multiple studies suggest that ILC2s are important in mice as well human subjects with Asthma. [10]. Interleukin-2 (IL-2) is an interleukin, a type of cytokine signaling molecule in the immune system. It is a 15.5–16 kDa protein that regulates the activities of white blood cells (leukocytes, often lymphocytes) that are responsible for immunity. Cells with the characteristics of ILC2s were first described as non-T, non-B cells that expanded on administration of IL-25.

4.2. Properties of IL2 cells

- ILCs comprise a newly described set of lymphocytes that produce an array of cytokines rivaling adaptive CD41 T cells.
- ILCs are activated in non-antigen-specific ways and, as innate cells, rapidly produce cytokines, including IL-5, IL-13, IFN- γ , and IL-17.
- These cytokines can direct the development of adaptive immunity or mediate immune responses independent of adaptive immunity.

NB. IL-33 plays important roles in type-2 innate immunity via activation of allergic inflammation-related eosinophils, basophils, mast cells, macrophages, and group 2 innate lymphoid cells (ILC2s).

4.3. Interactions of IL2, IL25, IL33 and TSLP

- TSLP, IL-25 and IL-33 are increasingly recognized to play important roles in pathophysiology of allergic diseases. Epithelium responds to various environmental factors by releasing key cytokines, such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-25.
- IL-2 is a pleiotropic cytokine,
- IL-2 is critical for the development of T regulatory cells (Tregs) in the thymus and the regulation, proliferation, and maintenance of Tregs in peripheral tissues, and is essential for maintaining the transcriptional program required for Treg function.
- This includes sustaining the expression of high levels of FoxP3, the key transcription factor that determines Treg identity [11].- IL-25, IL-33, and TSLP induce distinct activation profiles in ILC2s.

4.4. Targeting immune cells in the treatment of asthma

- Target early stages in the inflammatory cascade underlying allergic airway inflammation focus on changing and redirecting the initiation of type 2 inflammatory responses against allergens and certain viral agents and focus on upstream aspects of innate immunity that drive development of Th2-type.
- Allergic asthma, in which Th2-type immunity plays a central role, represents the majority of asthma cases, particularly in children.
- Novel class of therapeutic medications against Th2-type components, so-called biologicals.
- These are indicated for severe asthma in children, generally over six years of age when conventional medication is not effective.

Various biologicals targeting IgE, IL-4R alpha chain, IL-5, and IL-5R are Food and Drug Administration (FDA) approved. Currently there are five approved biologics for asthma – omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab that are FDA approved.

Table 1 Five FDA approved biologicals for asthma.

Therapy	Mechanism of Action	Indication	Dosing and Route	Adverse Effects
Omalizumab	Anti-IgE; prevents IgE from binding to its receptor on mast cells and basophils	≥6 yr old with moderate to severe persistent asthma, positive allergy testing, incomplete control with an ICS, and IgE: 30–1,300 IU/ml (United States, age 6–11 yr), 30–700 IU/ml (United States, age ≥ 12 yr), or 30–1,500 IU/ml (European Union)	0.016 mg/kg per IU of IgE (in a 4-wk period) administered every 2–4 wk s.c. (150–375 mg in United States; 150–600 mg in European Union)*	Black box warning: ~0.1–0.2% risk of anaphylaxis in clinical trials
Mepolizumab	Anti-IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	≥12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ≥ 150–300 cells/μl	100 mg s.c. every 4 wk	Rarely causes hypersensitivity reactions; can cause activation of zoster
Reslizumab	Anti-IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	≥18 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ≥ 400 cells/μl	Weight-based dosing of 3 mg/kg i.v. every 4 wk	Black box warning: ~0.3% risk of anaphylaxis in clinical trials
Benralizumab	Anti-IL-5; binds to IL-5 receptor α; causes apoptosis of eosinophils and basophils	≥12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ≥ 300 cells/μl	30 mg s.c. every 4 wk for three doses; followed by every 8 wk subsequently	Rarely causes hypersensitivity reactions
Dupilumab	Anti-IL-4R; binds to IL-4 receptor α; blocks signaling of IL-4 and IL-13	≥12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ≥ 150 cells/μl and/or F _{ENO} level ≥ 25 ppb	200 or 300 mg s.c. every 2 wk	Rarely causes hypersensitivity reactions; higher incidence of injection site reactions (up to 18%) and hypereosinophilia (4–14%)

Definition of abbreviations: AEC = absolute blood eosinophil count; F_{ENO} = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids.

*Upper limits exist for the dosing of omalizumab in patients with high IgE levels and increased weight.

Published in American journal of respiratory and critical care medicine 2019

M. McGregor, J. Krings, P. Nair, M. Castro

4.5. Childhood asthma control and available asthma control tools

4.5.1. Asthma Control

The National Asthma Education and Prevention Program guidelines highlight the importance of treating impairment and risk domains of asthma. The goals for therapy are as follows:

- Control asthma by reducing impairment through prevention of chronic and troublesome symptoms (eg, coughing or breathlessness in the daytime, in the night, or after exertion)
- Reduce the need for a short-acting beta2-agonist (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm)
- Maintain near-normal pulmonary function
- Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
- Satisfy patients' and families' expectations for asthma care

Reduction in risk can be achieved by preventing recurrent exacerbations of asthma and minimizing the need for emergency room visits and hospitalizations, and preventing progressive loss of lung function. For children, preventing reduced lung growth and providing optimal pharmacotherapy with minimal or no adverse effects is important.

- The domains of severity and control can be assessed in terms of impairment (frequency and intensity of symptoms, variations in lung function, and limitations of daily activities) and future risk (likelihood of exacerbations, progressive loss of lung function, or adverse effects from medications).

- Asthma can be considered to be well controlled if symptoms are present twice a week or less; rescue bronchodilator medication is used twice a week or less; there is nocturnal or early awakening; there are no limitations of work, school, or exercise; and the peak flow (PEF)/forced expiratory volume in 1 second (FEV1) is normal or at the personal best. Asthma control can be further classified as well controlled, not well controlled, and very poorly controlled as elegantly laid out in the National Heart, Lung and Blood Institute Expert Panel Report 3 (EPR3).

4.6. Clinical tools to assess asthma control in children

Patient-reported composite asthma control score instruments are attempts to capture the

Multidimensional nature of asthma control in a single numerical value. This enables the degree of asthma control to be compared across encounters. More than 17 composite instruments, each with at least 1 published validated study, are available. These instruments have comparable content and have been designed to measure asthma disease activity over a period of 1 to 4 weeks. Notably, none of them have been validated to assess an acute exacerbation.

- The commonly used validated tools are the Asthma Control Test (ACT), the Childhood Asthma Control Test (C-ACT),⁸ and the Asthma Control Questionnaire (ACQ).

The ACT contains 5 items, with a recall window of 4 weeks. The C-ACT is for use in children 4 through 11 years of age and consists of 4 pictorial items and 3 verbal items that are scored by the children and parents, respectively. It has been reported that children tend to assess their asthma control to be significantly lower than their parents do. The Asthma Control Questionnaire (ACQ) contains 6 items with a recall window of 1 week, supplemented by percentage of predicted FEV1 measurement. The Test for Respiratory and Asthma Control in Kids (TRACK)¹⁰ is a 5-question caregiver-completed questionnaire that determines respiratory control in children 0 to 5 years of age with symptoms consistent with asthma. Another less commonly used instrument is the Asthma Therapy Assessment Questionnaire (ATAQ), a 20-item parent-completed questionnaire exploring several domains, with 4 questions relating to symptom control and primarily used in research.

- Individual instruments contain 3 to 10 questions, and scoring varies by instrument [12].

4.7. GINA stepwise treatment of asthma in children

Your doctor will use a stepwise approach for treating your child's asthma. The goal is overall management with a minimum number of asthma attacks that require short-term treatment.

Short-acting bronchodilators (SABA) — provide immediate relief of asthma symptoms. Short-acting bronchodilators for asthma include albuterol (ProAir HFA, Ventolin HFA, others) and levalbuterol (Xopenex HFA). For children with mild, intermittent asthma symptoms, the short-acting medications may be the only treatment needed.

NB. -LAMA-Long Acting muscarinic antagonist e.g Tiotropium is a long-acting, anti-muscarinic agent, which is often referred to as an anticholinergic. Long-acting anti-muscarinic agent, often referred to as anticholinergic. Inhibits M3-receptors at smooth muscle, leading to bronchodilation. (GINA STEP FOUR OR HIGHER i.e Severe Asthma).

- LABA-Long-acting beta-agonists: The FDA has recommended LABAs be used ONLY in conjunction with inhaled steroids in asthma.
- Monoclonal antibodies such as mepolizumab, reslizumab and benralizumab have proven their benefit to reduce exacerbation rates in severe persistent eosinophilic asthma in published trials.
- The Global Strategy for Asthma Management and Prevention (GINA), the British Thoracic Society (BTS) and the American Thoracic Society are widely accepted documents concerning Asthma definition & management, released in the USA and in Europe, respectively.

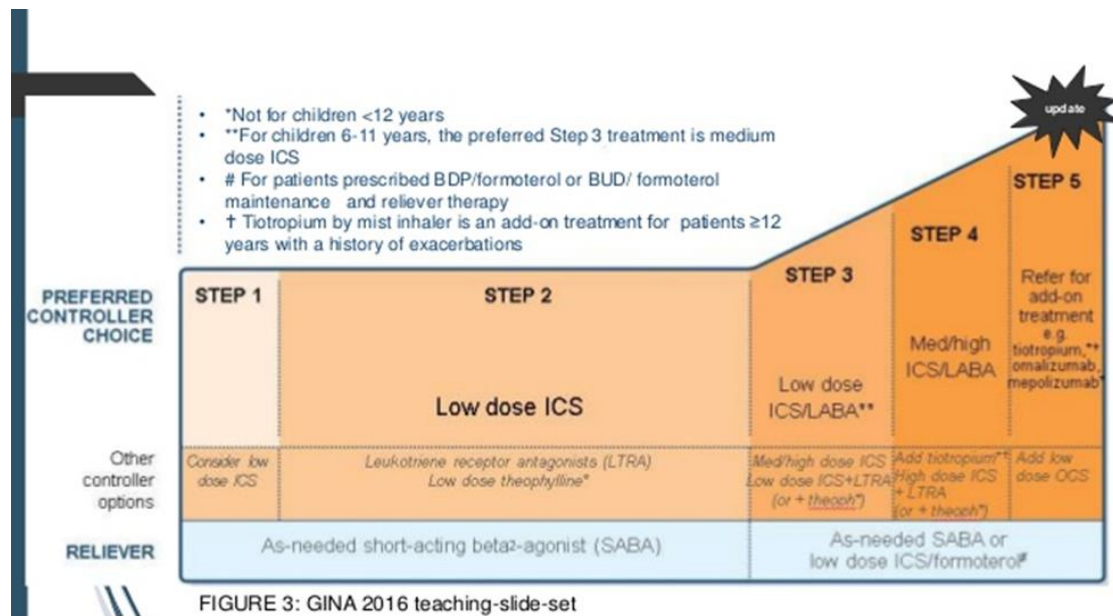


Figure 1 Gina stepwise treatment of asthma in children.

4.8. Differential diagnoses of childhood asthma: many diagnostic possibilities exist, but do not forget

- Aspiration Syndromes
- Bronchiolitis
- Bronchopulmonary Dysplasia
- Pediatric Airway Foreign Body
- Pediatric Allergic Rhinitis
- Pediatric Aspergillosis
- Pediatric Bronchiectasis
- Pediatric Gastroesophageal Reflux
- Primary Ciliary Dyskinesia
- Sinonasal Manifestations of Cystic Fibrosis

Tuberculosis
 HIV
 Enlarged Thoracic Lymphadenopathy
 Congestive Cardiac Failure

4.9. Spirometry and childhood asthma: obstructive flow volume loops

- Spirometry is commonly indicated for children with chronic cough, persistent wheezing, and for the diagnosis and monitoring of asthma.
- It must be included as a necessary component in reviewing asthma control where available, which is not the usual scenario in resource limited countries.-The spirometry test technique is similar in adults and children aged >6 years. The person performing the test should have the ability to identify common errors and to interpret the results of spirometry.[13] Appropriate equipment should be selected and prepared as needed (e.g. calibrated if required). The procedure should be explained to the patient in a friendly way. Patients should be asked if they have recently taken any medications such as bronchodilators or β-blockers, when they last had a meal (as heavy meals can affect performance of the test, possibly causing some restriction), and they should be advised not to wear tight or restrictive clothes that could interfere with the test. The patient's weight and height should be measured and entered into software along with the name, ID, age, sex, and race. The position of the patient for the test may be sitting (preferred) or standing. To perform a manoeuvre, a new disposable mouthpiece is attached to the spirometer and a nose clip is used or the patient is asked to pinch his/her nose. The next step is selection of the appropriate test manoeuvre (FVC, vital capacity (VC) or maximum voluntary ventilation (MVV)) from the spirometer and the test is performed accordingly. The FVC manoeuvre is most useful and is usually the only one performed.

- Steps for interpreting spirometry results include identification of common errors during the test by applying acceptability and repeatability criteria and then comparing test parameters with reference standards. Spirometry results depict only the pattern of ventilation, which may be normal, obstructive, restrictive, or mixed. The diagnosis should be based on both clinical features and spirometry results

4.10. Machine learning and severe asthma phenotypes in children/ distinguishing asthma phenotypes using machine learning approaches

Asthma is not a single disease, but an umbrella term for a number of distinct diseases, each of which are caused by a distinct underlying pathophysiological mechanism. These discrete disease entities are often labelled as 'asthma endotypes'. The discovery of different asthma subtypes has moved from subjective approaches in which putative phenotypes are assigned by experts to data-driven ones which incorporate machine learning. Unlike phenotypes, which are defined by sharing similar observable characteristics, endotypes may be defined as subtypes of a condition with overlapping clinical symptoms, but each being caused by a distinct underlying pathophysiological mechanism [14]. A paradigm shift brought by the recognition that childhood asthma is an aggregated diagnosis that comprises several different endotypes underpinned by different pathophysiology, coupled with advances in understanding potentially important causal mechanisms, offers a real opportunity for a step change to reduce the burden of the disease on individual children, families, and society. Data-driven methodologies facilitate the discovery of "hidden" structures within "big healthcare data" to help generate new hypotheses. These findings can be translated into clinical practice by linking discovered "phenotypes" to specific mechanisms and clinical presentations. Machine learning (ML) is the study of computer algorithms that improve automatically through experience. It is seen as a subset of artificial intelligence. Machine learning algorithms build a mathematical model based on sample data, known as "training data", in order to make predictions or decisions without being explicitly programmed to do so. For example, medical diagnosis, image processing, prediction, classification, learning association, regression etc. The intelligent systems built on machine learning algorithms have the capability to learn from past experience or historical data.

4.11. Stepwise treatment of childhood asthma

- The approach to asthma treatment is called stepwise.
- The dosage of medication used to control asthma must be monitored and sometimes "stepped up" or "stepped down" to achieve asthma control and then manage patient symptoms.
- Your Health Service Provider, will gradually increase or decrease – "step up" or "step down" – your medication doses until the best balance is found. It is extremely important to take your medications as directed.

5. Thermal bronchoplasty

Thermal bronchoplasty or bronchial thermoplasty (BT) Severe asthmatics have increased airway smooth muscle (ASM) responsible for bronchoconstriction and increased resistance of airway. BT is a novel treatment modality that uses radiofrequency energy to reduce ASM mass and resistance of airway. Heat is introduced into the airways through a tube. Thermal bronchoplasty requires 3 separate outpatient bronchoscopic procedures 3 weeks apart; one for each lower lobe of the lung and another for both upper lobes. Using a flexible bronchoscope, an Alair catheter is deployed into the airways, and controlled radiofrequency energy is delivered to a wire basket attached to the top of the catheter using the Alair controller system, in which thermal energy warms the lining of targeted airways to reduce airway smooth muscle (ASM) mass. Bronchial thermoplasty is intended to reduce, debulk, or partially eliminate smooth muscle tissue [15,16,17].

6. Conclusion

The recent Lancet Asthma Commission was predicated on the assumption that the term "asthma" was no more a diagnosis than is "arthritis" or "anemia." It is an umbrella term that should be used to describe a constellation of clinical symptoms, namely wheeze, breathlessness, chest tightness and cough, and should be followed by the question "what sort of asthma is this?" Dissecting out the individual asthmas is increasingly important as novel biologicals with different modes of action are increasingly being discovered. Phenotypes and endotypes of Childhood Asthma have been described.

Biomarkers and Biological drugs/agents should be made available to Sub-Saharan Countries, as biological agents have been proven to be cost effective in the management and treatment of severe asthma in Children.

Compliance with ethical standards

Acknowledgments

Professor Phillipa Musoke of Makerere University, Kampala, Uganda and Professor Peter Nyarango of the University of Namibia, Windhoek, Namibia. Priscilla Kobusinge, my wife, Children, Valeria, Rhonah, Ronnie & Victoria, for their encouragement.

Disclosure of conflict of interest

No conflict of interest is declared.

The author has no conflict of interest to declare. There are no personal or professional conflicts of interest regarding any aspect of this article.

References

- [1] American Academy of Asthma, Allergy and Immunology
- [2] Global Initiative on Asthma.GINA 2020.
- [3] Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012; 12: 204.
- [4] Kiboneka A, Levin M, Mosalakatane T, Makone I, Wobudeya E, Makubate B, Hopp R, Mazhani L, Kung SJ. Prevalence of asthma among school children in Gaborone, Botswana. *Afr Health Sci*. 2016 Sep;16(3):809-816.
- [5] Lai CKW, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009; 64: 476–483.
- [6] Robin J. Green*Pediatric Asthma in Southern Africa. *The Open Allergy Journal*. 2011; 4: 8-15.
- [7] Letamo G, Keetile M, Navaneetham K, Phatsimo M. Prevalence and correlates of self-reported chronic non-communicable diseases in Botswana: a cross-sectional study. *Int Health*. 2017 Jan;9(1):11-19.
- [8] Tadech Boonpiyathad, Zeynep Celebi Sözen et al. Immunologic mechanisms in asthma. *Semin Immunol*. 2019 Dec; 46: 101333.
- [9] Stanley J. Szeffler MD (Author), Francisco A Bonilla MD PhD (Author), Cezmi A Akdis (Author), Hugh Sampson (Author), Donald Y. M. Leung MD PhD (Editor). *Pediatric Allergy: Principles and Practice 3rd Edition*.
- [10] Sanhong Yu, PhD,Hye Young Kim, PhD,Ya-Jen Chang, PhD,Rosemarie H. DeKruyff, PhD, and Dale T. Umetsu, MD, PhD. Innate lymphoid cells and asthma. *J allergy clin immunol*. April 2014; 943-950.
- [11] Sarah H. Ross et al. Signaling and Function of Interleukin-2 in T Lymphocytes. *Annu Rev Immunol*. 2018 Apr 26; 36: 411–433.
- [12] Chitra Dinakar, MD, FAAP, Bradley E. Chipps, MD, FAAP. Clinical Tools to Assess Asthma Control in Children. *Pediatrics*. 2017;139(1):e20163438.
- [13] Rebecca Howard et al. Distinguishing Asthma Phenotypes Using Machine Learning Approaches. *Curr Allergy Asthma Rep*. 2015; 15: 38.
- [14] Mario Castro, Adalberto S. Rubin, Michel Laviolette. Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe AsthmaA Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial. *Am J Respir Crit Care Med*.181: 116–124.
- [15] Gerard Cox MB, Neil C. Thomson MD. Asthma Control during the Year after Bronchial Thermoplasty.
- [16] Torrego A, Solà I, Munoz AM, et al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. *Cochrane Database Syst Rev*. 2014 Mar 3; 3:CD009910.
- [17] After asthma: redefining airways diseases. *Lancet*. September 11, 2017.