https://doi.org/10.33591/sfp.45.6.ur

A SELECTION OF TEN CURRENT READINGS ON TOPICS RELATED TO ASTHMA AND INFLAMMATION – NEW UPDATES

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Selection of readings were made by A/Prof Goh Lee Gan

READING 1 – PATHOPHYSIOLOGY: UNDERSTANDING ASTHMA PHENOTYPES, ENDOTYPES, AND MECHANISMS OF DISEASE

Kuruvilla ME(1)(2), Lee FE(1)(3), Lee B(4)(5). Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019 Apr;56(2):219-233.

doi: 10.1007/s12016-018-8712-1. [Free full text]

Author information:
(1) Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, Department of Medicine, Emory University, 615 Michael St, NE Suite 205, Atlanta, 30322, GA,USA.
(2) Division of Pulmonary, Allergy & Immunology, Cystic Fibrosis, and Sleep, Department of Pediatrics, Emory University, 2015 Uppergate Dr. NE, Suite 326,Atlanta, GA, 30322, USA.
(3) Lowance Center for Human Immunology, Emory University, 615 Michael Street,Atlanta, 30322, GA, USA.
(4) Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, Department of Medicine, Emory University, 615 Michael St, NE Suite 205, Atlanta, 30322, GA,USA. gerald.b.lee@emory.edu.
(5) Division of Pulmonary, Allergy & Immunology, Cystic Fibrosis, and Sleep,Department of Pediatrics, Emory University, 2015 Uppergate Dr. NE, Suite 326,Atlanta, GA, 30322, USA. gerald.b.lee@emory.edu.

ABSTRACT
The model of asthma as a single entity has now been replaced by a much more complex biological network of distinct and interrelating inflammatory pathways. The term asthma is now considered an umbrella diagnosis for several diseases with distinct mechanistic pathways (endotypes) and variable clinical presentations (phenotypes). The precise definition of these endotypes is central to asthma management due to inherent therapeutic and prognostic implications. This review presents the molecular mechanisms behind the heterogeneity of airway inflammation in asthmatic patients. Asthma endotypes may be broadly regarded as type 2 (T2) high or T2-low. Several biologic agents have been approved for T2-high asthma,with numerous other therapeutics that are incipient and similarly targeted at specific molecular mechanisms. Collectively, these advances have shifted existing paradigms in the approach to asthma to tailor novel therapies.

READING 2 – PATHOPHYSIOLOGY: PATHOPHYSIOLOGICAL MECHANISMS OF ASTHMA

Bush A(1).Pathophysiological Mechanisms of Asthma. Front Pediatr. 2019 Mar 19;7:68.

doi: 10.3389/fped.2019.00068 [Free full text]

Author information:
(1)Departments of Paediatrics and Paediatric Respiratory Medicine, Royal Brompton Harefield NHS Foundation Trust and Imperial College, London, United Kingdom.

ABSTRACT
The recent Lancet commission has highlighted that "asthma" should be used to describe a clinical syndrome of wheeze, breathlessness, chest tightness, and sometimes cough. The next step is to deconstruct the airway into components of fixed and variable airflow obstruction, inflammation, infection and altered cough reflex, setting the airway disease in the context of extra-pulmonary co-morbidities and social and environmental factors. The emphasis is always on delineating treatable traits, including variable airflow obstruction caused by airway smooth muscle constriction (treated with short- and long-acting β-2agonists), eosinophilic airway inflammation (treated with inhaled corticosteroids) and chronic bacterial infection (treated with antibiotics with benefit if it is driving the disease). It is also important not to over-treat the untreatable, such as fixed airflow obstruction. These can all be determined using simple, non-invasive tests such as spirometry before and after acute administration of a bronchodilator (reversible airflow obstruction); peripheral blood eosinophil count, induced sputum, exhaled nitric oxide (airway eosinophilia); and sputum or cough swab culture (bacterial infection).Additionally, the pathophysiology of risk domains must be considered: these are risk of an asthma attack, risk of poor airway growth, and in pre-school children,risk of progression to eosinophilic school age asthma. Phenotyping the airway will allow more precise diagnosis and targeted treatment, but it is important to move to endotypes, especially in the era of

increasing numbers of biologicals. Advances in -omics technology allow delineation of pathways, which will be particularly important in TH2 low eosinophilic asthma, and also pauci-inflammatory disease. It is very important to appreciate the difficulties of cluster analysis; a patient may have eosinophilic airway disease because of a steroid resistant endotype, because of non-adherence to basic treatment, and a surge in environmental allergen burden. Sophisticated -omics approaches will be reviewed in this manuscript, but currently they are not being used in clinical practice. However, even while they are being evaluated, management of the asthmas can and should be improved by considering the pathophysiology of the different airway diseases lumped under that umbrella term, using simple, non-invasive tests which are readily available, and treating accordingly.

READING 3 – PATHOPHYSIOLOGY: NETOPATHIC INFLAMMATION IN COPD AND SEVERE ASTHMA

Uddin M(1)(2), Watz H(3)(4), Malmgren A(2), Pedersen F(3)(4)(5). NETopathic Inflammation in Chronic Obstructive Pulmonary Disease and SevereAsthma. Front Immunol. 2019 Feb 5;10:47.

doi: 10.3389/fimmu.2019.00047 [Free full text]

Author information:
(1) Respiratory Global Medicines Development, AstraZeneca, Gothenburg, Sweden.
(2) Respiratory, Inflammation and Autoimmunity, IMED Biotech Unit, AstraZeneca,Gothenburg, Sweden.
(3) Pulmonary Research Institute at LungenClinic, Großhansdorf, Germany.
(4) Airway Research Center North (ARCN), German Center for Lung Research (DZL),Großhansdorf, Germany.
(5) LungenClinic, Großhansdorf, Germany.

ABSTRACT
Neutrophils play a central role in innate immunity, inflammation, and resolution. Unresolving neutrophilia features as a disrupted inflammatory process in the airways of patients with chronic obstructive pulmonary disease (COPD) and severe asthma. The extent to which this may be linked to disease pathobiology remains obscure and could be further confounded by indication of glucocorticoids or concomitant respiratory infections. The formation of neutrophil extracellular traps (NETs) represents a specialized host defense mechanism that entrap and eliminate invading microbes. NETs are web-like scaffolds of extracellular DNA in complex with histones and neutrophil granular proteins, such as myeloperoxidase and neutrophil elastase. Distinct from apoptosis, NET formation is an active form of cell death that could be triggered by various microbial, inflammatory, and endogenous or exogenous stimuli. NETs are reportedly enriched in neutrophil-dominant refractory lung diseases, such as COPD and severe asthma. Evidence for a pathogenic role for respiratory viruses (e.g., Rhinovirus), bacteria (e.g., Staphylococcus aureus) and fungi (e.g., Aspergillus fumigatus) in NET induction is emerging. Dysregulation of this process may exert localized NET burden and contribute to NETopathic lung inflammation. Disentangling the role of NETs in human health and disease offer unique opportunities for therapeutic modulation. The chemokine CXCR2 receptor regulates neutrophil activation and migration, and small molecule CXCR2 antagonists (e.g., AZD5069, danirixin) have been developed to selectively block neutrophilic inflammatory pathways. NET-stabilizing agents using CXCR2 antagonists are being investigated in proof-of-concept studies in patients with COPD to provide mechanistic insights. Clinical validation of this type could lead to novel therapeutics for multiple CXCR2-related NETopathologies. In this Review, we discuss the emerging role of NETs in the clinicopathobiology of COPD and severe asthma and provide an outlook on how novel NET-stabilizing therapies via CXCR2 blockade could be leveraged to disrupt NETopathic inflammation in disease-specific phenotypes.

READING 4 – DIAGNOSIS – NEW APPROACHES TO ASTHMA DIAGNOSIS IN CHILDREN AND ADULTS

Saglani S(1)(2), Menzie-Gow AN(1)(3).Approaches to Asthma Diagnosis in Children and Adults.Front Pediatr. 2019 Apr 17;7:148.

doi: 10.3389/fped.2019.00148. [Free full text]

Author information:
(1) National Heart & Lung Institute, Imperial College London, London, United Kingdom.
(2) Department of Respiratory Paediatrics, Royal Brompton Hospital, London, United Kingdom.
(3) Department of Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom.

ABSTRACT
Although the hallmark features of asthma include reversible airflow obstruction, airway eosinophilia, and symptoms of recurrent wheeze associated with breathlessness and cough, it is a heterogeneous disease. The extent of the pathophysiological abnormalities are variable between patients. Despite this,until recently, asthma diagnosis had been made very simplistically predominantly from a clinical history and examination, and often a trial of medication such as short acting bronchodilators. The limitations of this approach

have become increasingly apparent with evidence of inappropriate over diagnosis, under diagnosis and misdiagnosis. Although there is no gold standard single test to make a diagnosis of asthma, there are several objective tests that can be used to support the diagnosis including physiological measures such as obstructive spirometry associated with bronchodilator reversibility and air way hyperresponsiveness. In addition, non-invasive tests of airway inflammation such as exhaled nitric oxide or peripheral blood eosinophils are important to identify those with an allergic or eosinophilic phenotype. Diagnostic guidelines reflect the importance of using objective tests to support a diagnosis of asthma, however practical application in the clinic may not be straightforward. The focus of this review is to discuss the need to undertake objective tests in all patients to support asthma diagnosis and not just rely on clinical features. The advantages, challenges and limitations of performing tests of lung function and air way inflammation in the clinic, the difficulties related to training and interpretation of results will be explored, and the utility and relevance of diagnostic tests will be compared in adults and children.

READING 5 – BIOMARKER: FRACTION EXHALED NITRIC OXIDE AS BIOMARKER OF ASTHMA CONTROL

de Abreu FC(1), da Silva Júnior JLR(2), Rabahi MF(1).The Fraction Exhaled Nitric Oxide as a Biomarker of Asthma Control. Biomark Insights. 2019 Jan 31;14:1177271919826550.

doi: 10.1177/1177271919826550 [Free full text].

Author information:
(1) Faculty of Medicine, Universidade Federal de Goias (UFG), Goiânia, Brazil.
(2) University Center Medical School, UniEVANGÉLICA, Anápolis, Brazil.

ABSTRACT
Introduction and Objective: The main goal of asthma treatment is to achieve and maintain clinical control of the disease. The exhaled fraction nitric oxide(FeNO) level is a biomarker of T-helper cell type 2 (Th2) inflammation of the airways. Our objective was to determine whether the FeNO level can be used to discriminate between patients with controlled, partially controlled, and uncontrolled asthma. Materials and Methods: The FeNO level and asthma control were evaluated in a retrospective and analytic cross-sectional study through data collected from asthmatic patients who were assessed by clinical history, asthma control, physical examination, spirometry, and FeNO level. Asthma control was determined by the criteria of the Global Initiative for Asthma and classified as controlled asthma, partially controlled asthma, and uncontrolled asthma. The FeNO values were classified as low (<25 ppb) or intermediate/high (≥25 ppb) based on the American Thoracic Society recommendations. Results: The symptoms of 81 asthmatic patients were classified as controlled (34 [42%] patients), partially controlled (27 [33.3%] patients), and uncontrolled (20[24.7%] patients). The FeNO level discriminated between the uncontrolled and controlled groups (P = .01) and between the uncontrolled and partially controlled groups (P = .01), but not between the controlled and partially controlled groups (P = .98). An FeNO level >30 ppb was associated with uncontrolled asthma(P = .0001) with an area under the receiver operating characteristic curve of 0.78 (95% confidence interval = 0.65-0.89). Conclusions: FeNO level could be helpful in determining asthma control as >30 ppb was associated with uncontrolled asthma.

READING 6 – FRACTIONAL EXHALED NITRIC OXIDE: ASSISTANCE IN MANAGEMENT OF UNCONTROLLED PERSISTENT ASTHMA

Zeiger RS(1)(2), Schatz M(1), Yang SJ(2), Chen W(2).
Fractional Exhaled Nitric Oxide-Assisted Management of Uncontrolled Persistent Asthma: A Real-World Prospective Observational Study. Perm J. 2019;23.

doi: 10.7812/TPP/18-109 [Free full text].

Author information:
(1)Department of Allergy, Clairemont Mesa Medical Center, San Diego, CA.
(2)Kaiser Permanente Southern California Research and Evaluation, Pasadena.

ABSTRACT
CONTEXT: The utility of fractional exhaled nitric oxide (FeNO) measurement in real-world asthma management requires investigation.

OBJECTIVE: To determine whether FeNO-assisted care added to standard asthma management improves asthma control in a managed care organization. DESIGN: Prospective observational study in patients aged 12 years and older with uncontrolled persistent

asthma identified during a scheduled visit to an Allergy Department that routinely used FeNO (FeNO-assisted care, n = 426) vs visits to 4 Allergy Departments that did not, but followed routine guideline-based care(standard care, n = 925). The FeNO-assisted care was based on FeNO level, asthma control status, and step-care level. MAIN OUTCOME MEASURES: Composite primary outcome was 1 or more asthma exacerbations or 7 or more dispensed canisters containing short-actingβ2-agonists in the follow-up year. Inverse probability of treatment weighting propensity scoring balanced covariates and multivariable regression analyses compared outcomes between groups. RESULTS: Compared with standard care, FeNO-assisted care was not associated with reducing the primary composite outcome (adjusted risk ratio = 0.94, 95%confidence interval = 0.69-1.29, p = 0.71), nor with a reduction in asthma exacerbations or dispensing of 7 or more short-acting β2-agonist canisters as separate outcomes. In an atopic subgroup with aeroallergen sensitization, the composite outcome was similar between groups, but the rate of asthma exacerbations was lower with FeNO-assisted treatment (adjusted rate ratio = 0.67,95% confidence interval = 0.49-0.91, p = 0.01).CONCLUSION: These findings suggest future studies of FeNO-assisted care should be directed at the atopic phenotype.

READING 7 – TREATMENT: TREATMENT OF SMALL AIRWAY DISEASE IN ASTHMA

Zinellu E(1), Piras B(2), Ruzittu GGM(3), Fois SS(4), Fois AG(5), Pirina P(6)(7).Recent Advances in Inflammation and Treatment of Small Airways in Asthma. Int J Mol Sci. 2019 May 28;20(11). pii: E2617.

doi: 10.3390/ijms20112617 [Free full text].

Author information:
(1) Respiratory Unit, Azienda Ospedaliero Universitaria (AOU), V.le San Pietro,07100 Sassari, Italy. elisabetta.zinellu@aousassari.it.
(2) Respiratory Unit, Department of Medical, Surgical and Experimental Sciences,University of Sassari, V.le San Pietro, 07100 Sassari, Italy.barbara.piras@aousassari.it.
(3) Respiratory Unit, Department of Medical, Surgical and Experimental Sciences,University of Sassari, V.le San Pietro, 07100 Sassari, Italy.giuliaruzittu@hotmail.com.
(4) Respiratory Unit, Department of Medical, Surgical and Experimental Sciences,University of Sassari, V.le San Pietro, 07100 Sassari, Italy.sara.solveig.fois@gmail.com.
(5) Respiratory Unit, Department of Medical, Surgical and Experimental Sciences,University of Sassari, V.le San Pietro, 07100 Sassari, Italy. agfois@uniss.it.
(6) Respiratory Unit, Azienda Ospedaliero Universitaria (AOU), V.le San Pietro,07100 Sassari, Italy. pirina@uniss.it.
(7) Respiratory Unit, Department of Medical, Surgical and Experimental Sciences,University of Sassari, V.le San Pietro, 07100 Sassari, Italy. pirina@uniss.it.

ABSTRACT
Small airways were historically considered to be almost irrelevant in the development and control of pulmonary chronic diseases but, as a matter of fact, in the past few years we have learned that they are not so "silent". Asthma is still a worldwide health issue due to the great share of patients being far from optimal management. Several studies have shown that the deeper lung inflammation plays a critical role in asthma pathogenesis, mostly in these not well-controlled subjects. Therefore, assessing the degree of small airways inflammation and impairment appears to be a pivotal step in the asthmatic patient's management. It is now possible to evaluate them through direct and indirect measurements, even if some obstacles still affect their clinical application. The success of any treatment obviously depends on several factors but reaching the deeper lung has become a priority and, for inhaled drugs, this is strictly connected to the molecule's size. The aim of the present review is to summarize the recent evidence concerning the small airway involvement in asthma, its physiopathological characteristics and how it can be evaluated in order to undertake a personalized pharmacological treatment and achieve a better disease control.

READING 8 – MANAGEMENT: NEW PARADIGMS IN ASTHMA MANAGEMENT

Valero A(1), Olaguibel J(2), Delgado J(3), Plaza V(4), Álvarez F(5), Molina J(6),Mascarós E(7), Quirce S(8). Dilemmas and New Paradigms in Asthma Management. J Investig Allergol Clin Immunol. 2019 Feb;29(1):15-23.

doi: 10.18176/jiaci.0345 [Free full text].

Author information:
(1) Sección de Alergología, Servicio de Neumología y Alergia, Hospital Clínic deBarcelona, Universitat de Barcelona, IDIBAPS, CIBER de Enfermedades Respiratorias(CIBERES), Spain.
(2) Unidad de Asma Grave, Servicio de Alergología, Complejo Hospitalario deNavarra, Pamplona and CIBER de Enfermedades Respiratorias (CIBERES).
(3) Unidad de Gestión Clínica de Alergología, Hospital Virgen Macarena, Sevilla,Spain.

(4) Servei de Pneumologia i Al.lèrgia, Hospital de la Santa Creu i Sant Pau,Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Universitat Autònomade Barcelona, Barcelona, Spain.
(5) Unidad de Asma, Unidad Médico-Quirúrgica de Enfermedades Respiratorias(UMQER), Hospital Universitario "Virgen del Rocio", Sevilla, Spain.
(6) CS Francia, Dirección Asistencial Oeste, Fuenlabrada, Madrid, Spain.
(7) Centro de Salud Fuente de San Luis, Departamento Hospital Dr Peset, Valencia, Spain.
(8) Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ) and CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain.

ABSTRACT
Asthma is one of the most common inflammatory diseases in the world. The main goal of treatment is to achieve optimal control. Although every patient is different, clinical practice guidelines can help physicians to manage the disease. However, the recommendations made by guidelines are not always identical, and the continuous release of new data on the various management strategies can mislead both patients and physicians. We aim to summarize the main controversies in management and treatment recommendations in asthma guidelines, revise the most recent scientific evidence, and pinpoint possible solutions. We do not issue new recommendations or challenge evidence-based guidelines. We concluded that more tools are necessary to achieve and measure optimal asthma control and to better assess the impact of asthma on patients' lives. Also essential is a more accurate appraisal of the short-term and long-term effectiveness and safety of asthma therapies and the possibilities of successful immunomodulation.

READING 9 – MONITORING: SYMPTOM SCORES, SPIROMETRY, AND OTHER PULMONARY FUNCTION TESTS FOR ASTHMA MONITORING

Gallucci M(1), Carbonara P(2), Pacilli AMG(2), di Palmo E(1), Ricci G(1), NavaS(2).Use of Symptoms Scores, Spirometry, and Other Pulmonary Function Testing forAsthma Monitoring.
Front Pediatr. 2019 Mar 5;7:54.

doi: 10.3389/fped.2019.00054.[Full free text]

Author information:
(1) Department of Pediatrics, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.
(2) Department of Specialistic, Diagnostic and Experimental Medicine (DIMES),University of Bologna, Alma Mater Studiorum, Bologna, Italy.

ABSTRACT
Asthma is a global problem affecting millions of people all over the world. Monitoring of asthma both in children and in adulthood is an indispensable tool for the optimal disease management and for the maintenance of clinical stability. To date, several resources are available to assess the asthma control, first is the monitoring of symptoms, both through periodic follow-up visits and through specific quality of life measures addressed to the patient in first person or to parents. Clinical monitoring is not always sufficient to predict the risk of future exacerbations, which is why further instrumental examinations are available including lung function tests, the assessment of bronchial hyper-reactivity and bronchial inflammation. All these tools may help in quantifying the future risk for each patient and therefore they potentially may change the natural history of asthmatic disease. The monitoring of asthma in children as in adults is certainly linked by many aspects, however the asthmatic child is a future asthmatic adult and it is precisely during childhood and adolescence that we should implement all the efforts and strategies to prevent the progression of the disease and the subsequent impairment of lung function. For these reasons, asthma monitoring plays a crucial role and must be particularly close and careful. In this paper, we evaluate several tools currently available for asthma monitoring, focusing on current recommendations emerging from various guidelines and especially on the differences between the monitoring in pediatric age and adulthood.

READING 10 – PROSPECTIVE OBSERVATIONAL COHORT STUDY: KOREAN CHILDHOOD ASTHMA STUDY

In Suh D(1), Song DJ(2), Baek HS(3) et al. Korean childhood asthma study (KAS): a prospective, observational cohort ofKorean asthmatic children.BMC Pulm Med. 2019 Mar 15;19(1):64.

doi: 10.1186/s12890-019-0829-3 [Free full text].

Author information:
(1) Department of Pediatrics, Seoul National University College of Medicine,Seoul, South Korea.
(2) Department of Pediatrics, Korea University College of Medicine, Seoul, South Korea.
(3) Department of Pediatrics, Hallym University Kangdong Sacred Heart Hospital,Seoul, South Korea.

(4) Department of Pediatrics, Soonchunhyang University School of Medicine,Bucheon, South Korea.
(5) Department of Pediatrics, Korea University Anam Hospital, Seoul, South Korea.
(6) Department of Pediatrics, Seoul National University Bundang Hospital,Seongnam, South Korea.
(7) Department of Pediatrics, National Health Insurance Service Ilsan Hospital,Ilsan, South Korea.
(8) Department of Pediatrics, Pediatric Allergy and Respiratory Center, Soonchunhyang University College of Medicine, Seoul, South Korea.
(9) Department of Pediatrics, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, South Korea.
(10) Department of Pediatrics, School of Medicine, The Catholic University of Korea, Bucheon St. Mary's Hospital, Bucheon, South Korea.
(11) Department of Pediatrics, Dankook University Hospital, Cheonan, South Korea.
(12) Department of Pediatrics, College of Medicine, Chungbuk National University, Cheongju, South Korea.
(13) Department of Pediatrics, Pusan National University Yangsan Hospital,Yangsan, South Korea.
(14) Department of Pediatrics, Gangnam CHA Medical Center CHA University School of Medicine, Seoul, South Korea.
(15) Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea.
(16) Department of Pediatrics, Mediplex Sejong hospital, Incheon, South Korea.
(17) Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.
(18) Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, South Korea.
(19) Asan Institute for Life Sciences, University of Ulsan College of Medicine,Seoul, South Korea.
(20) Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. jyu3922@gmail.com.
(21) Department of Pediatrics, Inje University Seoul Paik Hospital, Seoul, South Korea. ped3kim@gmail.com.
(22) Department of Pediatrics, School of Medicine, Inha University, Incheon, South Korea.
(23) Department of Pediatrics, School of Medicine, The Catholic University of Korea, Uijeongbu St. Mary's hospital, Uijeongbu, South Korea.
(24) Division of Allergy and Chronic Respiratory Diseases, Center for Biomedical Sciences, Korea National Institute of Health, Korea Centers for Disease Controland Prevention, Osong, South Korea.

ABSTRACT

BACKGROUND: Asthma is a syndrome composed of heterogeneous disease entities. Although it is agreed that proper asthma endotyping and appropriate type-specific interventions are crucial in the management of asthma, little data are available regarding pediatric asthma. METHODS: We designed a cluster-based, prospective, observational cohort study of asthmatic children in Korea (Korean childhood Asthma Study [KAS]). A total of 1000 Korean asthmatic children, aged from 5 to 15 years, will be enrolled at the allergy clinics of the 19 regional tertiary hospitals from August 2016 to December 2018. Physicians will verify the relevant histories of asthma and comorbid diseases, as well as airway lability from the results of spirometry and bronchial provocation tests. Questionnaires regarding subjects' baseline characteristics and their environment, self-rating of asthma control, and laboratory tests for allergy and airway inflammation will be collected at the time of enrollment. Follow-up data regarding asthma control, lung function, and environmental questionnaires will be collected at least every 6 months to assess outcome and exacerbation-related aggravating factors. In a subgroup of subjects, peak expiratory flow rate will be monitored by communication through a mobile application during the overall study period. Cluster analysis of the initial data will be used to classify Korean pediatric asthma patients into several clusters; the exacerbation and progression of asthma will be assessed and compared among these clusters. In a subgroup of patients, big data-based deep learning analysis will be applied to predict asthma exacerbation.

DISCUSSION:

Based on the assumption that asthma is heterogeneous and each subject exhibits a different subset of risk factors for asthma exacerbation, as well as a different disease progression, the KAS aims to identify several asthma clusters and their essential determinants, which are more suitable for Korean asthmatic children. Thereafter we may suggest cluster-specific strategies by focusing on subjects' personalized aggravating factors during each exacerbation episode and by focusing on disease progression. The KAS will provide a good academic background with respect to each interventional strategy to achieve better asthma control and prognosis.