# Oral Abstract Session 1

## Predictors and Clinical Correlates of Asthma

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OAS-1

## Increased Mortality in Patients with Corticosteroid-dependent Asthma: A Nationwide Population-based Study

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Introduction: Chronic systemic corticosteroid (CS) therapy is associated with an increased risk of mortality in patients with many chronic diseases. However, it has not been elucidated whether chronic, systemic CS therapy is associated with increased mortality in patients with asthma.
Objective: To determine the effects of chronic, systemic CS therapy on long-term mortality in adult patients with asthma.
Design, Setting, and Participants: A population-based matched cohort study of men and women aged 18 years or older with asthma was performed using the Korean National Health Insurance Service database from 2005 to 2015.
Exposures: Chronic use of systemic CS (≥six months) during the baseline year
Main Outcomes and Measures: All-cause mortality during the up to 10-year follow-up period. Hazard ratio (HR) with 95% confidence interval (CI) for mortality among patients in the CS-dependent cohort relative to those in the CS-independent cohort.
Results: The baseline cohort included 466,941 patients with asthma, of whom 8,334 were CS-dependent and 456,607 were CS-independent. After 1:1 matching, 8,334 subjects with CS-independent asthma were identified. The HR of mortality associated with CS-dependent asthma relative to CS-independent asthma was 2.17 (95% CI, 2.04-2.31). In patients receiving low-dose CS, the HR was 1.84 (95% CI, 1.69-2.00), and that for those receiving high-dose CS was 2.56 (95% CI, 2.35-2.80).
Conclusions: In this real-world, clinical practice, observational study, chronic use of systemic CS was associated with increased risk of mortality in patients with asthma, with a significant dose-response relationship between systemic CS use and long-term mortality.

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Key Words: Corticosteroid, Severe asthma, Mortality

OAS-2

## Characteristics of Severe Asthma Patients Treated with Biologics in Real-World: Findings From Korean Severe Asthma Registry (KoSAR)

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Severe asthma has high morbidity and healthcare utilization. However, treatment options for these patients are limited. Recently, a new paradigm for severe asthma treatment is emerging with introduction of novel biologics. Currently, several biologics such as mepolizumab, reslizumab, and omalizumab have been approved in Korea and began to be prescribed for severe asthma. The aim of this study is to figure out the current status of biologics use in real-world clinics in Korea.
Korea Severe Asthma Registry (KoSAR), the largest representative severe asthma cohort in Korea, was established in 2011 and the patients were enrolled from 28 university hospitals nationwide in Korea (n=495). Severe asthma was defined according to modified European Respiratory Society/ American Thoracic Society criteria. Among them, independent Biologic Registry (BR) was established to evaluate clinical features of the patients treated with biologics (n=41). In this study, we analyzed various clinical characteristics and courses of the patients treated with biologics in real-world clinics in Korea.
Mepolizumab was prescribed in 31 patients and reslizumab in 10 patients in BR. The mean age of the patients was 51.2±12.8 years, which was lower than that of whole patients in KoSAR (62.3±14.0). The asthma onset age was 35.7±18.3 years, which was also lower than that of whole KoSAR (44.8 ±16.3). The number of exacerbations over the past year was 1.1±1.7. Mean FVC, FEV1 and FEV1/FVC values were 74.5±15.6%, 66.8±18.4% and 70.2±11.4%, respectively. Mean blood eosinophil count was 695.2±823.3. There were no reported side effects except mild burning sensation in only one case.
It is important to know the status of biologic treatment for severe asthma in Korea not only because the medical environment can vary in each country but also because analyzing the characteristics of the patients may be helpful to improve the management of severe asthma in real-world clinical practice.

Key Words: Severe asthma, Biologics, Eosinophilic asthma

OAS-3

## Clinical Care Program for Childhood Asthma (CCP-Childhood Asthma): The Combination of Multidisciplinary Care Team with Smart Asthma E-care for Improving Asthma Controlled in Children

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Purpose: Asthma is a common childhood chronic respiratory disease and the cause of hospitalization. Samitivej Children's Hospital provides Clinical Care Program for Childhood Asthma (CCP-Childhood Asthma) with a multidisciplinary team and using smart tool, Asthma E-care, to help improving asthma controlled.
Methods: CCP-Childhood Asthma team were set up including Allergists, Pulmonologists, nurses at OPD, ER, ward & PICU, pharmacists & physiatrists. Enrolled asthmatic children were treated and followed-up as to clinical pathway and were engaged in Childhood Asthma Camp aiming to educate about disease to caregivers, together with workshop for inhaler use, self-assessment with asthma action plan, and allergen avoidance. We developed a tool using informative technology to assist communication between patients-family and CCP-Childhood Asthma, Asthma E-care, to assess clinical asthma controlled in patients, adjust controlled medication, and alarm need for emergency visit when exacerbation. This tool aims to prevent unscheduled visit to emergency room or hospitalization from asthma exacerbation. The following outcomes: rate of asthma exacerbation, hospitalization from asthma exacerbation, and scheduled visit and follow-up rate were collected monthly and were analyzed for percentage change quarterly, and for monitoring.
Results: From launching this program since 2015, rate of asthma exacerbation dropped from 9.7% in Q4/2015 to 1.1% in Q3/2018; hospitalization from asthma exacerbation dropped from 1.2% in Q1/2016 to 0.5% in Q3/2018; and scheduled visit and followed-up by Asthma E-care were increase from 56.4% in 2015 to 80.1% in 2018. No any patient was admitted in PICU or having severe asthma exacerbation. Rate of annual influenza vaccination of asthmatic children in the program ranged from 59.5% to 62% with about 10% of influenza infection yearly.
Conclusion: Care of children with asthma, with the combination of comprehensive multidisciplinary team care and smart Asthma E-care tool, help improving quality of care for these children to achieve clinical asthma controlled.

OAS-4

## Asthma Control Test Reflects Not Only Lung Function but Also Airway Inflammation in Children with Stable Asthma

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Objective: Various numerical asthma control tools have been developed to distinguish different levels of symptom control. We aimed to examine whether the asthma control test (ACT) is reflective of objective findings such as lung function, fractional exhaled nitric oxide (FeNO), and laboratory data in patients with stable asthma.
Methods: We included patients who were enrolled in the Korean Childhood Asthma Study. ACT, spirometry, blood tests, and FeNO were performed in patients after stabilization of their asthma. We examined differences among spirometry parameters, blood tests, and FeNO according to control status as determined by ACT and investigated for any significant correlations.
Results: The study population consisted of 441 subjects. Spirometry showed that forced expiratory volume in one second (FEV1), forced expiratory flow between 25%-75% of forced vital capacity, and FEV1/forced vital capacity were all significantly higher in the controlled asthma group. Likewise, FeNO and percent-change in FEV1 were both significantly lower in the controlled asthma group. In blood tests, the eosinophil fraction was significantly lower in the controlled asthma group while white blood cell count was significantly higher in the controlled asthma group. Lastly, among the various factors analyzed, only provocative concentration of methacholine causing a 20% fall in FEV1 significantly correlated with ACT score.
Conclusion: ACT is useful as part of the routine evaluation of asthmatic children and should be used as a complement to existing tools such as spirometry and FeNO measurement.

Key Words: Asthma control test, Lung function, Airway inflammation

OAS-5

## Obstruction Phenotype as a Predictor of Asthma Severity in Children with Asthma

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**Background:** It is suggested that an air-trapping obstruction and the airflow limitation pattern of the obstruction could be used to identify obstruction phenotypes that are indicators of risk for asthma severity and instability. This study was performed to determine respiratory phenotypes in children with asthma and their associations with allergic sensitization and biomarkers.
**Methods:** The study population included 147 asthmatic children, aged 6-18 years. We measured the periostin levels in serum and performed methacholine and exercise provocation challenges. The Asthma Control Test (ACT) was performed. An air-trapping obstruction phenotype was defined as a forced vital capacity (FVC) z-score of less than -1.64 or an increase in FVC of 10% of the predicted value or greater with bronchodilation. The airflow limitation phenotype had a forced expiratory volume in 1 second (FEV1)/FVC z-score of less than -1.64 but not an air-trapping obstruction phenotype. The no airflow limitation or air-trapping (none) phenotype had neither an air-trapping obstruction phenotype nor an airflow limitation phenotype.
**Results:** The 147 asthmatic children were divided into three phenotypes: asthmatics with the air-trapping obstruction phenotype (n=41), asthmatics with the airflow limitation phenotype (n=40), and asthmatics with the none phenotype (n=66). The air-trapping obstruction phenotype was associated with significantly greater asthma severity and lower ACT scores, as compared to the airflow limitation phenotype and none phenotype. The air-trapping obstruction phenotype had significantly greater levels of the maximum decrease in FEV1 after exercise. No significant differences were found in methacholine PC20, allergic sensitization, fraction of exhaled nitric oxide, and serum periostin levels between the three phenotypes.
**Conclusions:** Obstruction phenotypes as defined by routine spirometric measurements could be predictors of asthma severity and asthma control.

**Key Words:** Asthma, Children, Obstruction phenotype

OAS-6

## Changes in Forced Oscillation Technique (FOT) Parameters during 4-Year-Follow-Up in Children and Adolescents with Asthma: Possible Indices for Lung Function Decline in Asthma

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**Purpose:** Forced oscillation technique (FOT) is a noninvasive method for measuring respiratory impedance, resistance (R) and reactance (X). It has a potential to evaluate unique aspects in asthma that spirometry doesn't. Since lung function decline in asthma children has been reported to be related to the development of COPD, we investigated changes in FOT parameters in relation with changes in maximal expiratory flow at 50 % of the forced vital capacity (MEF50) that expresses obstruction of the small airways in spirometry.
**Methods:** Subjects were children with asthma who were followed for 4 years at our institution. Clinical data and spirometry and FOT (MostGraph®) were retrospectively reviewed. The subjects were divided into 3 groups based on changes in average data of MEF50 over the 4-year-period($\Delta$MEF50): ① PLUS group, $\Delta$MEF50 were larger than plus 5%, ② NC group, $\Delta$MEF50 were within 5 %, ③ MINUS group, $\Delta$MEF50 were less than minus 5%.
**Results:** A paired 542 data set (PLUS:134, MINUS:254, NC:154) were analyzed.R5 and R20 significantly increased (deteriorated) in MINUS group and increased even in NC group, however, were unchanged in PLUS group. The tendency was more evident in subjects in whom initial MMF50 <60% of predicted values.
**Conclusions:** The results suggest that 'no change' in the small airway index of spirometry in childhood may not mean 'stable' but may indicate loss of lung function development, which may lead to further deterioration in later life. FOT may detect the fine changes of lung function development.

OAS-7

## Real-World Evidence of Lung Function Declines in Severe Asthma

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**Introduction:** The pathogenic mechanism of severe asthma (SA) and its clinical outcome are not clearly understood. To further investigate SA, we established an integrated long-term real-world database, ICARUS (Immune/inflammatory disease Common data model Augmentation for Research Union System), by combining the electronic medical records and the biomarker data.
**Methods:** We enrolled 2,037 adult asthmatics (649 severe asthmatics and 1,388 nonsevere asthmatics) who had been treated with standardized medications following the GINA guideline from 1994 to 2017. Severe asthmatics were defined as those who had experienced at least 4 times of asthma exacerbation over 2 years despite step 4/5 medications. Demographic characteristics were compared, and lung function changes including FEV1 and FEV1/FVC were compared using linear regression. A Lasso regression model was implemented to identify predictive variables for SA.
**Results:** Severe asthmatics were older and had higher female proportion. In addition, severe asthmatics showed greater falls of FEV1% and FEV1/FVC (significantly rapid decline) for 15 years' follow-up period than nonsevere asthmatics. The Lasso logistic regression suggested that several potential biomarkers (blood/sputum eosinophil counts, sputum neutrophils, serum periostin, serum total IgE) could predict SA.
**Conclusion:** Progressive lung function declines were demonstrated in severe asthmatics (even they had been treated in a tertiary asthma center) in the real-world practice. Further studies will be needed to validate suggested biomarkers and to develop future interventions to prevent lung function decline.

**Key Words:** Severe asthma, Lung function, Biomarker

OAS-8

## SOX18 as a Potential Biomarker is Associated with Asthma Exacerbation

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**Background:** Asthma characterized by airway hyperresponsiveness, increased inflammatory cells, and fibrosis and angiogenesis. SRY-related HMG-box 18 (SOX18) is an important transcription factor involved in the development of cardiovascular and lymphatic vessels during embryonic development and wound-healing processes. SOX18 remains to be clarified in asthma.
**Objective:** In this study we aimed to elucidate the role of SOX18 in the pathogenesis of bronchial asthma.
**Methods:** Using an established mouse model of ovalbumin (OVA)-induced chronic allergic asthma, we investigated whether SOX18 is involved in pathogenesis of asthma. Airway hyperresponsiveness (AHR) was measured and bronchoalveolar lavage fluid was collected, lung tissue was processed for protein and RNA, and hematoxylin and eosin stain. Collagen was measured by trichrome stain and sircol assay. SOX18 level checked in lung human microvascular endothelial cells (HMVEC-L) and normal human bronchial epithelial (NHBE) cells treated with house dust mite (HDM). Moreover, we observed SOX18 levels in blood from asthmatic patients between stable and exacerbated state. Results: The chronic asthma mice showed that SOX18, PROX1, COUP-TFII, mucous gland hyperplasia and collagen deposition in lung tissue were significantly increased after OVA challenge. SOX18 protein in HMVEC-L and NHBE cells was increased following HDM treatment. PROX1 and COUP-TFII protein in HMVEC-L were decreased and increased in NHBE cells following HDM treatment. SOX18 in blood from exacerbated asthmatics was increased compared with those from stable asthmatics.
**Conclusion:** These results suggesting that SOX18 may be associated with asthma exacerbation and can be a biomarker for asthma

**Key Words:** SOX18, Bronchial asthma, Airway remodeling

OAS-9

## The Extract Mixture of Ivy Leaves and Coptidis Rhisoma Attenuates the Steroid-Resistant Asthmatic Manifestation in Mice

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Severe asthma with steroid resistance is prevalent in fewer than 10% of total patients with asthma but is associated with substantial morbidity and mortality and a significant fraction of the health care costs among asthmatic patients. Although better asthma management needs a refined understanding of disease heterogeneity and mechanisms in relation to clinically significant outcomes, the mechanisms contributing to steroid-resistant asthma, especially non-type 2 immune response, are less clear. Thus, the therapeutic options are also limited for patients with severe asthma. Classically, ivy leaves dry extract is registered as an expectorant in patients with respiratory diseases associated with productive cough. In this, study, we evaluated the pharmacologic efficacy of the extract mixture of ivy leaves and Coptidis rhisoma on both eosinophilic and neutrophilic severe asthma manifestations using the OVA-LPS induced neutrophilic asthma animal model and the Aspergillus fumigatus (Af)-induced eosinophilic asthma animal model. Interestingly, treatment with the extract mixture of ivy leaves and Coptidis rhisoma attenuated both endotypes of steroid-resistant asthmatic manifestations including airway hyperresponsiveness, pathologic changes, and the production of pro-inflammatory cytokines, although the effective dose of the combined extract was different slightly according to the asthma endotype. These findings suggest that uncontrolled asthma phenotypes despite corticosteroid therapy might benefit from the treatment with the extract mixture of ivy leaves and Coptidis rhisoma regardless of the endotype: type 2 and non-type 2 asthma.

Key Words: Ivy leaves extract, Steroid-resistant asthma

OAS-10

## Empagliflozin and Dulaglutide are Effective against Obesity-induced Airway Hyperresponsiveness and Fibrosis in A Murine Model

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**Backgrounds:** Patients with asthma with obesity experience severe symptoms, are unresponsive to conventional asthma treatment, and lack proper pharmacotherapy. Empagliflozin and dulaglutide, developed for diabetes, reduce weight, decrease insulin resistance, and exert synergistic effects. We evaluated the efficacy of empagliflozin, dulaglutide, and their combination on obesity-induced airway hyperresponsiveness (AHR) and lung fibrosis using a murine model.
**Methods:** We assigned C57BL/6J mice to five groups: control, high-fat diet (HFD), and HFD with empagliflozin, dulaglutide, or both. Mice received a 12-week HFD, empagliflozin (5 days/week, oral gavage), and dulaglutide (once weekly, intraperitoneally).
**Results:** Both drugs significantly attenuated HFD-induced weight increase and abnormal glucose metabolism, and co-treatment was more effective. Both drugs significantly alleviated HFD-induced AHR, increased macrophages in bronchoalveolar lavage fluid (BALF), and co-treatment was more effective on AHR. HFD-induced lung fibrosis was decreased by both drugs alone and combined. HFD induced interleukin (IL)-17, transforming growth factor (TGF)-$\beta$1, and IL-1$\beta$ mRNA and protein expression, which was significantly reduced by empagliflozin, dulaglutide, and their combination. Tumour necrosis factor (TNF)-$\alpha$ and IL-6 showed similar patterns without significant differences. HFD-enhanced T helper (Th) 1 and Th17 cell differentiation was improved by both drugs.
**Conclusions:** Empagliflozin and dulaglutide could be a promising therapy for obesity-induced asthma and showed synergism in combination.

Key Words: Asthma, Airway hyperresponsiveness, Obesity

OAS-11

# The Effect of Intratracheally Treated Mesenchymal Stem Cells on Murine Asthma Model Via Modulation of Macrophage Activation

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**Background:** Treatment options for severe asthma are limited and some patients with severe asthma need new treatment option to control over the symptom. Mesenchymal stem cells (MSCs) have not only tissue repairing effect but also immune-regulatory activity, which has been applied for chronic inflammatory disorders including asthma. However, the exact mechanisms of MSCs on diverse immune cells has not been clearly validated.
**Objective:** We aimed to investigate the potential therapeutic benefits of intratracheal stem cell instillation by using the murine ovalbumin model.
**Method:** Six-week-old female BALB/c mice were divided into four groups: control group, MSC-treated group, ovalbumin (OVA) asthma group, and MSC-treated OVA asthma group. Mice were sensitized and challenged with OVA with or without intratracheal treatment of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) during the challenge periods. The airway hyperresponsiveness (AHR) was measured by lung resistance in response to aerosolized methacholine and flow cytometry was used to study macrophages, dendritic cells, T cells, and innate lymphoid cells.
**Result:** The number of inflammatory cells, especially eosinophils and macrophages as well as AHR were significantly reduced with MSC treatment in OVA/MSC group. Flow cytometry revealed that intratracheal MSC instillation reduced M2 differentiation, APC-like alveolar macrophages, and MHCII+ dendritic cells. Among M2 macrophage subsets, M2c population was the majority of the M2 population, with the largest decrease with intratracheal MSCs instillation. In the OVA/MSC group, the expressions of IL-12 and iNOS, M1 markers, were enhanced. While the expression of Arg1, typical M2 marker was upregulated, expression of relm-$\alpha$, a protective M2 marker, showed further enhancement by hUC-MSCs.
**Conclusion:** hUC-MSC has an anti-asthmatic effect on the OVA model and this effect seems to be mediated by the modulation of M1/M2 differentiation in part.

**Key Words:** Asthma, Mesenchymal stem cells, Macrophage differentiation