European Review for Medical and Pharmacological Sciences 2015; 19: 942-949

Can we modulate asthma maintenance treatment level with disease seasonal variations?

B. SPOSATO, M. SCALESE[1], G. MOSCHINI[2], M.G. MIGLIORINI

Unit of Pneumology, "Misericordia" Hospital, Grosseto, Italy
[1]Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy
[2]Emergency Department, "S. Giovanni di Dio" Hospital, Orbetello, Italy

Abstract. – Asthma can have clinical seasonal fluctuations due to different exposure factors. The analysis of our data and literature confirm a seasonal trend of asthma severity. In this brief review, authors discuss the possibility to adapt maintenance therapy level to clinical seasonal fluctuations, by increasing treatment in some seasons to prevent exacerbations and by decreasing it in others, when symptoms are low, in order to minimize costs and maximize safety.

Literature and our data (concerning studies carried out in areas with a temperate climate) indicate that asthma severity is reduced in summer while it tends to increase in the other seasons.

Authors conclude that a preventive increasing maintenance treatment level during the season when we know that patients worsen (starting some weeks before symptom worsening) may reduce asthma exacerbation risks. On the contrary, a summer treatment reduction, in patients that improve during this period, may be considered only in asthma phenotypes with a benign disease course in time.

Key Words:
Asthma, Season, Treatment, Management, Prescription, Exacerbation.

Introduction

Asthma Seasonality

It is already known that asthma can show clinical seasonal fluctuations, especially in areas with temperate climate. In fact, in spring, when airborne pollen exposure increases, and in winter, when allergenic indoor exposure and the risk of viral/bacterial airway infection are higher, a greater use of asthma medication prescriptions and emergency department visits were documented[1-4]. In addition, climate factors and air pollution, which change with the alternation of the seasons, can influence asthma status often favouring its exacerbation[5-10]. The impact of season variations can also be detected on the magnitude of airway hyperresponsiveness. Higher risks of more severe airway hyper-responsiveness (AHR) were found in autumn/winter and spring, whereas a lower risk was described in summer[11-13]. Allergens, bacteria, viruses and other environmental factors can interact with a defective airway epithelium. In fact, they activate the epithelial-mesenchymal trophic unit (EMTU) that, consequently, starts the cascade of events leading to airway inflammation[14], with a worsening of previous clinical conditions, especially in winter and spring. On the contrary, during the summer, a lower exposure to allergen/viral/bacterial/environmental factors may reduce the level of airway inflammation and consequently lead to an improvement of asthma symptoms. The above described changes in clinical asthma status may be responsible for a seasonal variation in the maintenance and relief treatment level (as shown also by our data), which can be lowered when asthmatics do not experience symptoms and increased when symptoms worsen[4,15,16].

Our data also seem to confirm such trend. In our area, in fact (as shown in Figure 1), in the three-year period 2010-2012, the frequency of admissions to emergency rooms for asthma exacerbations (ICD-9 493.XX code) was clearly related to seasons, both in children/adolescents (aged between 5 and 17 years) and young adults (aged between 18 and 40 years), with a significantly lower exacerbation rate in summer compared to the other seasons. Comparisons of monthly data were performed using the chi-square test. P values < 0.05 were considered statistically significant. The statistical package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. A parallel trend (more marked in children/adolescents) was observed in the number of mainte-

Corresponding Author: Bruno Sposato, MD; e-mail: bsposat@tin.it

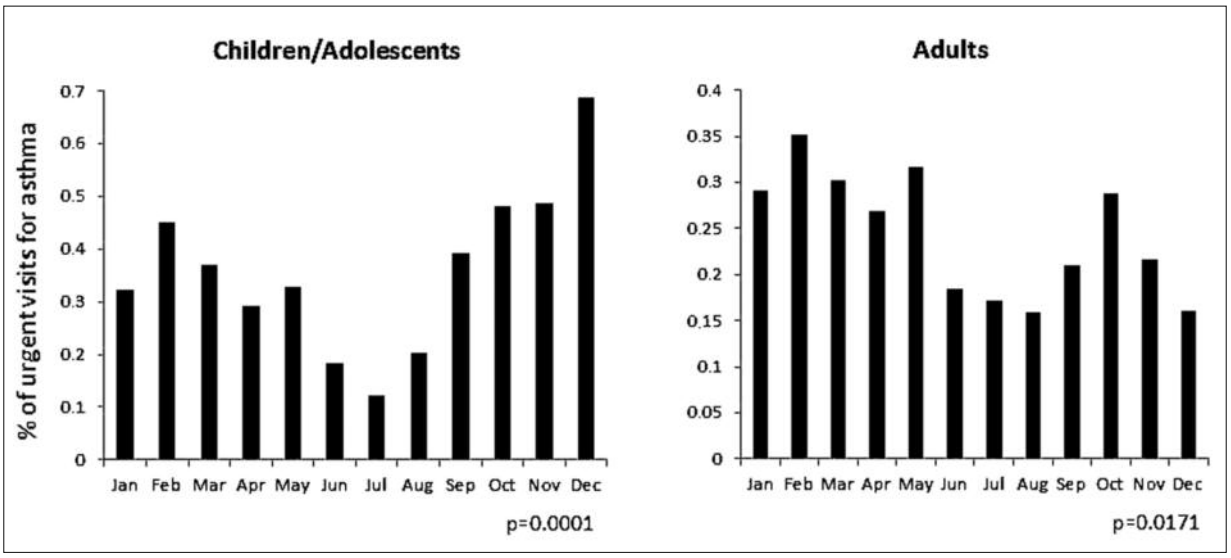

Figure 1. Percentage of monthly emergency room accesses observed in children/adolescents (> 5 and < 17 years) and adults (≥18 and ≤ 40 years) in a three-year period between 2010 and 2012 observed in the Grosseto area, Tuscany. All accesses to Emergency departments recorded with an ICD-9 493.XX code were considered. The number of admissions to emergency departments for asthma was described as a percentage of the total number of emergency admittances. A χ^2 test was used to compare the monthly emergency room visit trends The use of the data for the purpose of this article was approved by the local Ethical Committee.

nance (inhaled corticosteroids alone or in fixed association with long acting bronchodilators and montelukast) and relief (short-acting bronchodilators and oral corticosteroids) asthma medication prescriptions (Figure 2).

Also another study[15], performed on children, confirmed that emergency department and outpatient visits were lower during the summer, increased in September, peaked in October or November and remained high during the winter. The autumnal peak may be due to a greater exposure to dust mite or viral infections that occur early in autumn when children go back to school thus increasing infection transmission[17-19]. According to our data, except for the October peak, the worsening of symptoms and asthma exacerbations were more restricted in winter and spring in adults. Another study found a higher worsening of symptoms, urgent care utilization and prednisone use in winter than in the other seasons in adults[16]. The greater diffusion of infections in winter may also explain the higher emergency room accesses and asthma medication use in adults in this season. Whereas, a greater airborne pollen exposure in Spring, mainly due to grass pollen[1,2], may explain the urgent visit and prescription peak in this season observed in our area.

Such season variability may induce a modulation of therapy on the basis of "asthma seasonality". In fact, during the summer, the poor symptom perception, may lead patients (and probably also some physicians) to reduce or even interrupt treatment when symptoms turn to low intensity or disappear completely. More than 50% of asthmatics have a poor adherence to treatment[20,21] also because they are low symptom perceivers. GINA guidelines[22] envisage the step-up and the step-down of treatment according to symptom control but they do not specifically refer to a possible seasonal treatment modulation.

Such asthma seasonal trend has led us to try and give an answer to the following question: is it sensible to adapt the therapy level to the seasonal fluctuations of asthma severity?

Asthma Treatment Reduction in Summer

As already said, according to our data and to those reported in literature[4,15-19], a reduction of asthma drug prescriptions was detected in summer both in adults and especially in children, as a consequence of an improvement or a complete disappearance of symptoms in this season, which is probably accompanied also by a better pulmonary function. This improvement may even involve a treatment discontinuation in this season. Physicians, and above all children's parents, may also be responsible for a wrong asthma management as they may worry to over-treat

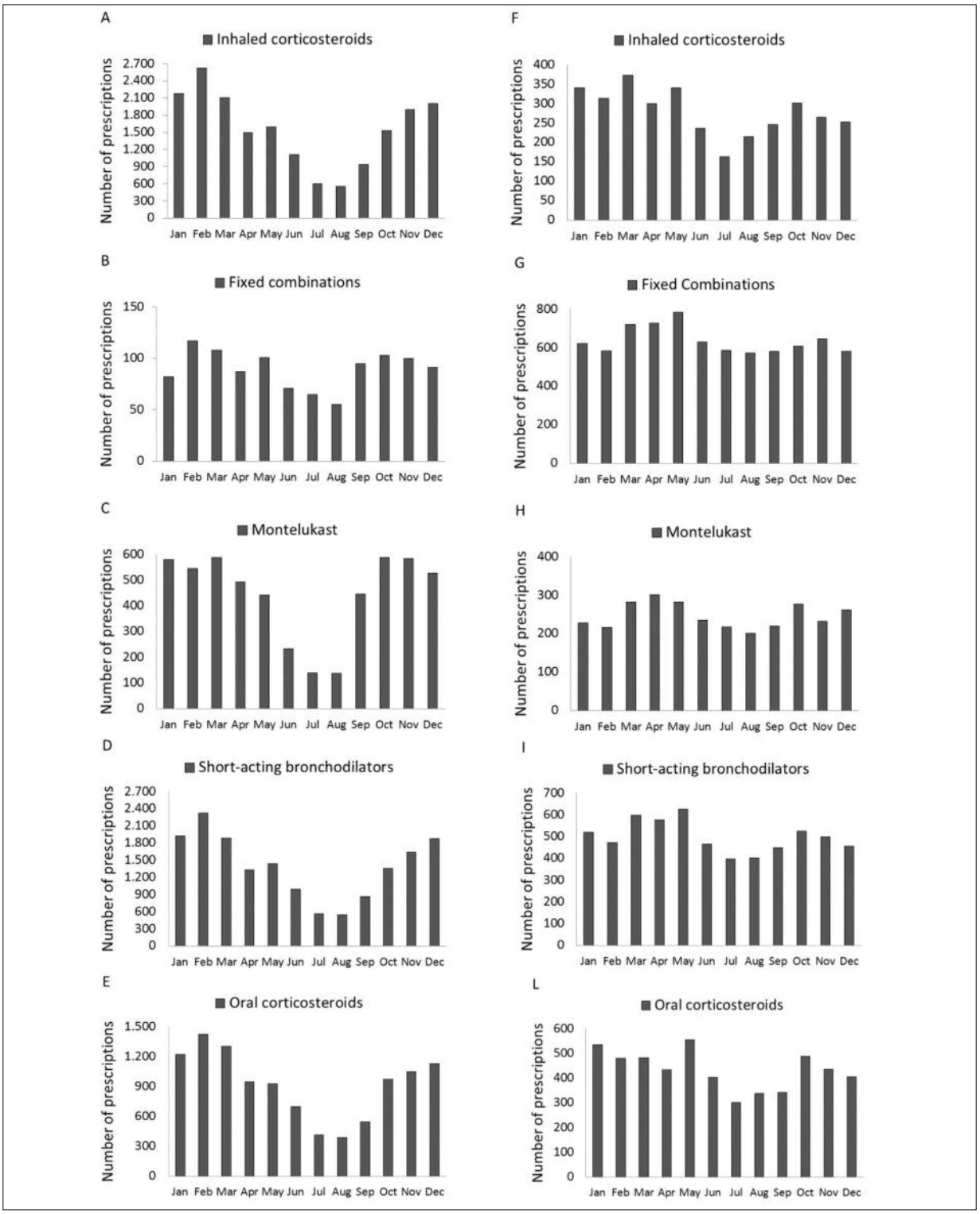

Figure 1. Number of monthly maintenance and relief asthma medication prescriptions in children/adolescents (> 5 and < 17 years) ***(A-E)*** and adults (≥18 and ≤ 40 years) ***(F-L)*** in a three-year period between 2010 and 2012 observed in the Grosseto area, Tuscany, Italy. All the prescriptions recorded by our territorial pharmacy with R03 and HO_2 Anatomical Therapeutic Chemical code (ACT) were considered. Beclometasone, ciclesonide, mometasone, fluticasone and budesonide were categorized as "inhaled corticosteroids", whereas beclometasone/formoterol, fluticasone/salmeterol and budesonide/formoterol were considered as "fixed combinations". Betamethasone, prednisolone and prednisone were considered together as oral corticosteroids and salbutamol as a short-acting bronchodilator. The use of the data for the purpose of this article was approved by the local Ethical Committee.

children. In fact, they may be inclined to reduce or even suspend treatment when children feel better. The summer hiatus may contribute to increases in health care use and asthma medication prescriptions in the autumn[15,17-19]. This seems not to implicate subjects that had taken inhaled corticosteroids in August[18]. A lower level of airway inflammation during the summer probably tends to increase progressively, if not treated, until it becomes, after a while, symptomatic during the autumn/winter seasons. This may also be valid for adults. Therefore, it may be incorrect to reduce, or even more, suspend treatment completely when symptoms are low or disappear at least in some patients. Airway inflammation is always present in asthma also when symptoms are low or when asthma is intermittent in subjects with normal lung function[23,24]. Airway inflammation seemed not to regress completely even when a higher level of inhaled corticosteroids were used[25]. On the other hand, symptoms may be under-perceived despite a remarkable level of airway inflammation. In fact, a variable percentage of 26-38% of controlled asthma patients showed an increased level of fractioned exhaled nitric oxide (FeNO)[26,27]. In addition, it must be underlined that, according to GINA guidelines[22], the goal (when treating asthmatics) should be to achieve and maintain an optimal clinical control. Asthmatics with a FEV_1 <80%, but without symptoms, should be considered as partly controlled patients[22]. These subjects should not reduce their treatment level. In fact, in children and adults with persistent asthma symptoms, daily and regular ICSs treatment was more efficacious than intermittent ICSs therapy in improving lung function, airway inflammation, asthma control and relief drug use[28]. We still do not know whether therapy modulation can be considered in subjects with normal pulmonary function and poor symptoms perception.

Asthma Phenotypes and Possible Treatment Seasonal Modulations

As already said, dropping treatment may foster an increase of inflammation and therefore the development of airway remodelling and consequently pulmonary function decline. In fact, some clinical trials have highlighted a slowing down of FEV_1 decline with a continuous inhaled corticosteroid treatment[29-33]. As remodelling can already be observed during childhood[34,35], treatment should never be reduced. Probably, an adulthood asthma level may be a consequence of a suboptimal infancy therapy level. However, admittedly, remodelling does not develop in all subjects[36,37] and, therefore, a certain amount of asthmatics may show a benign course of the disease. These subjects may be subjected to a seasonal modulation of treatment. In fact, there are different asthma phenotypes. Some authors[38] have identified two main phenotypes: one with reversible (RAO) and one with fixed airflow obstruction (FAO). The first one may show a low or no FEV_1 decline, whereas the second one, may have an accelerated loss in lung function[36]. In addition, the RAO phenotype may be characterized by a higher response to treatment, whereas the FAO phenotype may show a moderate/low or no response to therapy. In FAO patients, the inflammatory pattern can vary from neutrophilic - with a CD8 T-cell involvement similar to the one found in COPD - to eosinophilic - with a CD4 Th2 cell involvement akin to that of asthma patients without FAO[38]. The neutrofilic pattern determines a more accelerated lung function decline non-responsive to treatment, whereas the eosinophilic pattern may be fairly/partially responsive to therapy with a possible slowing down of FEV_1 decline. In fact, the improvement in lung function after 8 weeks was observed only in the Th2 inflammatory phenotype but not in the non-Th2 type[39]. Therefore, seasonal modulation of treatment, on the basis of symptom perception, may be considered in asthmatics with reversible airflow obstruction, who might be highly responsive to treatment and who might reduce/suspend treatment during the summer. They are usually subjects with normal (or almost normal) pulmonary function. On the contrary, FAO asthmatics with a prevalent Th2-phenotype (eosinophilic pattern) should not reduce the treatment level when symptoms are low because a prolonged treatment decreasing and, above all, a therapy suspension may increase airway inflammation and consequently influence remodelling and facilitate lung function decline. Furthermore, this reduction/suspension of treatment can favour disease exacerbations that can accelerate lung function decline[40,41]. On the contrary, asthmatics who show an accelerated FEV_1 decline (neutrophilic pattern), might not be responsive to a continuous and high-dosage anti-inflammatory treatment and the course of their disease might not be affected at all. A continuous reduction and/or suspension of therapy starting since childhood may affect the pulmonary function of declining subjects' adulthood. Unfortunately, nowadays, we do not have a

clinical marker that may allow us to identify subjects with "normal" pulmonary function who may develop a fixed obstruction and whose reduction/suspension of treatment may have negative effects in time. Therefore, it might not be advisable either to reduce or stop treatment during summer without asthma phenotyping.

As already stated, there are asthmatics who have a poor symptom perception and who are inclined to follow a reduced level of therapy or no therapy at all. It seems that up to 60% of asthmatics are not able to detect changes in their lung function[42]. Probably, the measurement of fractional exhaled nitric oxide (FeNO) may help us. Recent evidence indicates that FeNO identifies T-helper cell type 2 (Th2)-mediated airway inflammation with a high positive and negative predictive value for identifying corticosteroid responsive airway inflammation[43,44]. Therefore, FeNO and especially the alveolar fraction of exhaled NO, may be a reliable adjunct to traditional tests in the assessment of asthma[43,44]. Importantly, it may be useful for identifying and excluding ICS-responsive airway inflammation. Collectively, asthma managed using FeNO seems to be associated with lower exacerbation rates compared with clinical algorithms alone. Furthermore, FeNO may be useful in identifying patients at risk for future impairment or loss of asthma control during reduction/cessation of ICS treatment[43,44]. Therefore, FeNO measurement may be the instrument that would permit us to modulate treatment at least in some patients.

Preventive Increase of Maintenance Treatment During Adverse Seasons

On the basis of our results, we realized that there is a worsening of symptoms in some seasons. An increase in the use of salbutamol, oral corticosteroids and fixed combinations was observed especially in young adults in spring. This is in accordance with the study of Canova et al.[1] confirming that, especially in Southern Europe, young asthmatics sensitized to grass were more likely to report asthma attacks between March and June. All this suggests a possible preventive increase in the level of treatment (either increasing the dosage of inhaled corticosteroids, or adding montelukast or long-acting bronchodilators) in allergic asthmatics in some seasons. For example, a treatment increase should be introduced some weeks before the spring in grass sensitized asthmatics and/or before the autumn in house dust mite sensitized subjects and carried on for the whole season. Vice versa, the therapy level might be taken back to baseline or even reduced (perhaps only in some subjects, as we have already observed) in the other seasons, for example in summer (like in Southern Europe) when the allergy burden in pollens and in house dust mite is low. This approach could prevent exacerbations during the spring, when exposure to pollen is high and therefore the inflammation level is higher too. Besides, a drug dosage reduction might minimize costs and maximize safety. Our data seem to support what already stated. In fact, a higher use of asthma medications during the winter seems to have repercussions on the following season with a reduced amount of asthma relief medication prescriptions (short-acting bronchodilators and oral corticosteroids) especially in children. This appears to be in line with another study observing that subjects who were prescribed inhaled corticosteroids in August showed a lower incidence of medical contacts in September[18]. Guidelines do not consider the possibility to preventively increase the level of treatment, but support that a step-up of therapy should be performed when a worsening of symptoms/control is under way[19]. On the other hand, guidelines report that acute asthma is preventable with optimal control of chronic asthma. On this respect, there is evidence that higher doses of inhaled corticosteroids might be effective in preventing progression to severe exacerbations or the use of oral corticosteroids[45,46]. Also a daily, rather than intermittent, treatment resulted more effective in terms of exacerbation reduction, as cited before[28]. In addition, in patients with chronic asthma and seasonal aeroallergen sensitivity, montelukast treatment provided significant asthma control during the allergy season compared with placebo[47]. Therefore, when dealing, for example, with a patient who worsens yearly in spring, we may temporarily increase his treatment level some weeks in advance and then continue for the whole season to reduce the risk of exacerbations during the following months. Perhaps, using a combination of low values of ACT and FEV_1 with high levels of FeNO, when subjects are stable, may predict a near future exacerbation[48-50] and therefore help us establish when treatment should be increased.

Conclusions

There are asthma seasonal variations that must be considered in the disease management. Asthma seasonality may favour a poor adher-

ence to treatment. A seasonal maintenance treatment modulation may be a valid approach in order to minimize costs and maximize safety. However, a treatment reduction in summer can be suggested only for a restricted number of patients who have a normal pulmonary function and a benign disease course in time. Probably, only when we succeed in characterizing the various asthma phenotypes, this approach will probably be taken into account. An increasing preventive treatment level during the season when patients worsen (starting some weeks before symptom worsening) may reduce asthma exacerbation risks.

Acknowledgements

We thank Ms Angela Giovannoni for collecting the necessary data for this study. We thank also Prof. Piero Angelo Lenzi for his linguistic editing.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Canova C, Heinrich J, Anto JM, Leynaert B, Smith M, Kuenzli N, Zock JP, Janson C, Cerveri I, De Marco R, Toren K, Gislason T, Nowak D, Pin I, Wist M, Manfreda J, Svanes C, Crane J, Abramson M, Burr M, Burney P, Jarvis D. The influence of sensitisation to pollens and moulds on seasonal variations in asthma attacks. Eur Respir J 2013; 42: 935-945.
2) Erbas B, Chang JH Dharmage S, Ong EK, Hyndman R, Newbigin E, Abramson M. Do level of airborne grass pollen influence asthma hospital admissions?. Clin Exp Allergy 2007; 37: 1641-1647.
3) Moineddin R, Nie JX, Domb G, Leong AM, Upshur RE. Seasonality of primary care utilization for respiratory diseases in Ontario: a time-series analysis. BMC Health Serv Res 2008; 8: 160.
4) Koster ES, Raaijmakers JA, VijVerberg SJ, van der Ent CK, Maitland-van der Zee AH. Asthma symptoms in pediatric patients: differences throughout the seasons. J Asthma 2011; 48: 694-700.
5) Sposato B, Scalese M, Pammolli A, Pareo C, Scala R. Influence of outdoor temperature and humidity on the methacholine challenge test. Aerobiologia 2013; 29: 187-200.
6) Chen CH, Xirasagar S, Lin HC. Seasonality in adult asthma admission, air pollutant levels, and climate: A population-based study. J Asthma 2006; 43: 287-292.
7) Xrasagar S, Lin HC, Liu TC. Seasonality in pediatric asthma admission: The role of climate and environmental factors. Eur J Ped 2006; 165: 747-752.
8) Ivey MA, Simeon DT, Monteil MA. Climatic variables are associated with seasonal acute asthma admissions to accident and emergency room facilities in Trinidad, West Indies. Clin Exp Allergy 2003; 33: 1526-1530.
9) Mireku N, Wang Y, Ager J Reddy RC, Baptist AP. Changes in weather and the effects on pediatric asthma exacerbations. Ann Allergy Asthma Immunol 2009; 103: 220-224.
10) Kim S, Kim Y, Lee MR, Kim J, Jung A, Park JS, Jang AS, Park SW, Uh ST, Choi JS, Kim YH, Buckley T, Park CS. Winter season temperature drops and sulfur dioxide levels effect on exacerbation of refractory asthma in South Korea: a time-trend controlled case-crossover study using soonchunhyang asthma cohort data. J Asthma 2012; 49: 679-687.
11) Sposato B, Scalese M, Pammolli A, Scala R, Naldi M. Season can influence the results of the methacholine challenge test. Ann Thorac Med 2012; 7: 61-68.
12) Fruchter O, Yigla M. Seasonal variability of the methacholine challenge test. J Asthma 2009; 46: 951-954.
13) Joseph L, Picard E, Dayan B, Goldberg S. Methacholine challenge test results in children are season dependent. Lung 2013; 191: 553-557.
14) Holgate ST. The airway epithelium is central to the pathogenesis of asthma. Allergol Int 2008; 57: 1-10.
15) Van Dole KB, Swern AS, Newcomb K, Nelsen L. Seasonal patterns in health care use and pharmaceutical claims for asthma prescriptions for preschool- and school-aged children. Ann Allergy Asthma Immunol 2009; 102: 198-204.
16) Janson SL, McGrath KW, Covington JK, Baron RB, Lazarus SC. Objective airway monitoring improves asthma control in the cold and flu season. Chest 2010; 138: 1148-1155.
17) Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. J Allergy Clin Immunol 2006; 117: 557-562.
18) Julious SA, Campbell MJ Bianchi SM, Murray-Thomas T. Seasonality of medical contacts in school-aged children with asthma: association with school holidays. Public Health 2011; 125: 769-776.
19) Lin S, Jones R, Liu X, Hwang SA. Impact of the return to school on childhood asthma burden in New York State. Int J Occup Environ Health 2011; 17: 9-16.
20) Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I, Accordini S, Almar E, Bugiani M, Vermeire P, De Marco R; Therapy and health economics group of the European community respiratory health survey. Asthma control in Europe: a real-world evalu-

ation based on an international population-based study. J Allergy Clin Immunol 2007; 120: 1360-1367.

21) Latry P, Pinet M, Labat A, Magand JP, Peter C, Robinson P, Martin-Latry K, Molimard M. Adherence to anti-inflammatory treatment for asthma in clinical practice in France. Clin Ther 2008; 30: 1058-1068.

22) Global Strategy for Asthma Management and Prevention (GINA) 2011; available online on www.ginasthma.org, downloaded on date 10/06/2012.

23) Vignola AM, Chanez P, Campbell A, Campbell AM, Souques F, Lebel B, Enander I, Bousquet J. Airway inflammation in mild intermittent and in persistent asthma. Am J Respir Crit Care Med 1998; 157: 403-409.

24) Bartoli ML, Bacci E, Carnevali S, Cianchetti S, Dente FL, Di Franco A, Giannini D, Taccola M, Vagaggini B, Paggiaro PL. Clinical assessment of asthma severity partially corresponds to sputum eosinophilic airway inflammation. Respir Med 2004; 98: 184-193.

25) Pavord ID, Jeffery PK, Qiu Y, Zhu J, Parker D, Carlsheimer A, Nava I, Barnes NC. Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol. J Allergy Clin Immunol 2009; 123: 1083-1089.e7.

26) Alvarez-Gutiérrez FJ, Medina-Gallardo JF, Pérez-Navarro P, Martín-Villasclaras JJ, Martin Etchegoren B, Romero-Romero B, Praena-Fernández JM. Comparison of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control according to the Global Initiative for Asthma (GINA). Arch Bronconeumol 2010; 46: 370-377.

27) Khalili B, Boggs PB, Shi R, Bahna S. Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide. Ann Allergy Asthma Immunol 2008; 101: 124-129.

28) Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. Cochrane Database Syst Rev 2013; 2: CD009611.

29) Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, O'Byrne PM; START Investigators Group. The inhaled steroid treatment as regular therapy in early asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy Clin Immunol 2008; 121: 1167-1174.

30) Lange P, Scharling H, Ulrik CS, Vestbo J. Inhaled corticosteroids and decline of lung function in community residents with asthma. Thorax 2006; 61: 100-104.

31) Dompeling E, van Schayck CP, van Grunvsen PM, van Herwaarden CL, Akkermans R, Molema J, Folgering H, van Weel C. Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids. A 4-year prospective study. Ann Intern Med 1993; 118: 770-778.

32) O'Byrne PM, Lamm CJ, Busse WW, Tan WC, Pedersen S; START Investigators Group. The effects of inhaled budesonide on lung function in smokers and non-smokers with mild persistent asthma. Chest 2009; 136: 1514-1520.

33) O'Byrne PM, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, Pauwels RA; START Investigators Group. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. Chest 2006; 129: 1478-1485.

34) Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the childhood asthma management program. Am J Respir Crit Care Med 2004; 170: 234-241.

35) Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, Sears MR. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV1/vital capacity ratio: a longitudinal population study from childhood to adulthood. Am J Respir Crit Care Med 2002; 165: 1480-1488.

36) Contoli M, Baraldo S, Marku B, Casolari P, Marwick JA, Turato G, Romagnoli M, Caramori G, Saetta M, Fabbri LM, Papi A. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. J Allergy Clin Immunol 2010; 125: 830-837.

37) Connolly CK, Prescott RJ. The Darlinghton and Northallerton long term asthma study: pulmonary function. BMC Pulm Med 2005; 5: 2.

38) Tubby C, Harrison T, Todd I, Fairclough L. Immunological basis of reversible and fixed airways disease. Clin Sci 2011; 121: 285-296.

39) Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV. T-helper Type 2–driven Inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med 2009; 180: 388-395.

40) O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. START Investigators Group. Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med 2009; 179: 19-24.

41) Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J 2007; 30: 452-456.

42) Kendrick AH, Higgs CM, Whitfield MJ, Laszlo G. Accuracy of perception of severity of asthma: patients treated in general practice. Br Med J 1993; 307: 422-424.

43) Mahr TA, Malka J, Spahn JD. Inflammometry in pediatric asthma: a review of fractional exhaled nitric oxide in clinical practice. Allergy Asthma Proc 2013; 34: 210-219.

44) Scichilone N, Battaglia S, Taormina S, Modica V, Pozzecco E, Bellia V. Alveolar nitric oxide and asthma control in mild untreated asthma. J Allergy Clin Immunol 2013; 13: 1513-1517.

45) Reddel HK, Barnes DJ. Pharmacological strategies for self-management of asthma exacerbations. Eur Respir J 2006; 28: 182-199.

46) Oborne J, Mortimer K, Hubbard RB, Tattersfield AE, Harrison TW. Quadrupling the dose of inhaled corticosteroids to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. Am J Respir Crit Care Med 2009; 180: 598-602.

47) Busse WW, Casale TB, Dykewicz MS, Meltzer EO, Bird SR, Hustad CM, Grant E, Zeldin RK, Edelman JM. Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity. Ann Allergy Asthma Immunol 2006; 96: 60-68.

48) Gelb AF, Flynn Taylor C, Shinar CM, Gutierrez C, Zamel N. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. Chest 2006; 129: 1492-1499.

49) Sato R, Tomita K, Sano H, Ichihashi H, Yamagata S, Sano A, Yagamata T, Miyara T, Iwanaga T, Muraki M, Tohda Y. The strategy for predicting future exacerbation of asthma using acombination of the Asthma Control Test and lung function test. J Asthma 2009; 46: 677-682.

50) Ko FW, Hui DS, Leung TF, Chu HY, Wong GW, Tung AH, Ngai JC, Ng SS, Lai CK. Evaluation of the asthma control test: a reliable determinant of disease stability and a predictor of future exacerbations. Respirology 2012; 17: 370-378.