

RESEARCH LETTER

Relationship between immune parameters during a severe exacerbation in allergic asthmatic children and asthma outcomes in the following year

To the Editor,

Despite improvement in asthma maintenance treatment, exacerbations remain important issues. They are markers of severe asthma but can also occur in mild asthma.¹ Viruses, and mainly rhinoviruses (RVs), are the main triggers, and they may interact with aeroallergen-specific immunoinflammatory pathways in atopic patients.^{2,3} Some studies have suggested that these episodes could be related to an alteration of innate immune defenses and particularly a defective production of type I and III interferons (IFN).⁴ Most of them were ex vivo studies, consisting of the inoculation of respiratory viruses on primary cultures of bronchial epithelial cells from various asthma patients, with various ranges of ages, disease severity, and atopy background.^{5,6} In 72 school-aged children with allergic asthma, we previously reported an impaired antiviral and cytokine response in both sputum and plasma during severe exacerbation, mostly triggered by virus (62%), not related with an altered expression of pattern recognition receptors (PRR) on peripheral blood mononuclear cells (PBMCs).⁷ This defective antiviral response was more pronounced in a subgroup of patients prone to viral re-infection at steady state. These findings need to be confirmed by other studies further determining the characteristics of patients more prone to develop virus-induced severe exacerbation and disease progression.⁹ Indeed, long-term consequences are unknown, and to our knowledge, no study has yet assessed the relationship between inflammatory and antiviral response during severe exacerbations and future asthma outcomes.

The aim of this study was to explore this relationship in the first year following severe exacerbation in our previously cited cohort of school-aged children.⁷ We also compared asthma characteristics recorded at baseline and asthma outcomes at 1 year.

Full description of the population, methods, and immune parameters has been previously published.^{2,7} Briefly, school-aged (6–16 years) children with atopic asthma were included during severe exacerbation (exacerbation), defined by the need for hospitalization and a course of systemic corticosteroids (prednisolone, methylprednisolone), then assessed 8 weeks later (steady state: absence of ongoing exacerbation and course of general steroids) and every 4 to 6 months, including a visit at 1 year (1 year), according to the guidelines. Following the exacerbation, maintenance treatment was prescribed or adjusted according to the guidelines.⁷ Adherence and inhaler technique were assessed at each visit. Control was rated

and classified into the following categories: well-controlled, partly controlled or uncontrolled, according to the Global Initiative for Asthma (GINA) guidelines and Asthma Control Tests (ACTs)/paediatric ACTs (<12 years) (well-controlled asthma if score ≥ 20).⁸ During follow-up, severe exacerbations, defined by the need for systemic corticosteroids and/or hospitalization, were recorded. Lung function tests were performed at steady state and 1-year visits, according to European Respiratory Society (ERS)/American Thoracic Society (ATS) recommendations.

As previously described, during exacerbation (within 48 hours following the hospitalization and initiation of general corticosteroids) and at steady state, plasma samples, nasal secretions, and spontaneous or induced sputum were collected.⁷ Virus identification was performed using a commercially available multiplex reverse transcription-polymerase chain reaction (RT-PCR). Levels of interleukin (IL) IL-5, IL-22, C-C motif chemokine ligand (CCL) CCL5 (R&D Systems), IFN- γ , IL-1 β , IL-6, IL-17A, IL-23, IL-29 (eBiosciences), and IFN- β (Elabsciences Biot.) in plasma and sputum fluids were measured by ELISA. To analyse the activation and the expression of PRR, Toll-like receptor 3 (TLR3), melanoma differentiation-associated protein 5 (MDA5), and retinoic acid-inducible gene I (RIG-I) within blood dendritic cells (DCs) and monocytes, PBMC were incubated with isotype-matched control antibodies for lymphocytes and granulocytes, DCs, and monocytes. The expression of TLR3, MDA5, and RIG-I (Santa-Cruz Biotechnology) was estimated after intracellular indirect staining and analysed by flow cytometry.

At 1-year visit, patients were classified into three groups according to asthma outcomes: (a) good responders: no exacerbation during follow-up and well-controlled asthma according to GINA guidelines; (b) partial responders: no more than one severe exacerbation during follow-up and/or partly controlled asthma; (c) poor responders: ≥ 2 severe exacerbations during follow-up and/or uncontrolled asthma.

Qualitative variables were reported as the number or the percentage whereas continuous variables were expressed as median (interquartile range [IQR]). Normality was assessed graphically and via the Shapiro-Wilk test. Poor responders were compared to the others (partial and good responders) using the chi-square test or Fisher's exact test for qualitative variables and using Mann-Whitney test for continuous variables. All statistical tests were done at the two-tailed α level of 0.05 using SAS software, release 9.4 (SAS Institute).

TABLE 1 Population characteristics according to 1-year outcomes

	Total population n = 62	Good and partial responders (n = 40)	Poor responders (n = 22)	P ^a
Characteristics at baseline				
Age (years)	8.7 (7.6; 11.4)	8.7 (7.6; 10.4)	9.5 (7.6; 12.6)	.19
Male	44 (71.0)	29 (72.5)	15 (68.2)	.72
Age at asthma diagnosis	2.0 (1.0; 5.7)	1.5 (1.0; 5.0)	2.0 (0.5; 6.0)	.99
Allergic rhinitis	42 (67.7)	26 (65.0)	16 (72.7)	.53
Food allergy	10 (16.1)	8 (20.0)	2 (9.1)	.47
Atopic dermatitis	26 (41.9)	15 (37.5)	11 (50.0)	.34
≥2 severe exacerbations in the past year	25 (40.3)	14 (35.0)	11 (50.0)	.25
Maintenance treatment	29 (46.7)	15 (37.5)	14 (63.6)	.048
ICS dose (fluticasone eq, µg/day)	400 (250; 500)	400 (250; 500)	500 (250;1000)	.37
LABA	24/28 (85.7) ^b	13/15 (86.7)	11/13 (84.6) ^b	NA
Exacerbation				
Duration of hospitalization (days)	4.0 (3.0; 5.5)	4.0 (3.0; 5.0)	5.0 (3.5; 6.0)	.046
Duration of oxygen therapy (days)	2.5 (1.0; 4.5)	2.5 (1.0; 4.0)	3.0 (2.0; 5.0)	.35
Virus	40 (64.5)	30 (75.0)	10 (45.5)	.020
Rhinovirus	33 (53.2)	26 (65.0)	7 (31.8)	.012
Number of cells in sputum (n × 10 ³ /mg)	6.3 (3.4; 20.0)	5.9 (3.5; 16.9)	10.3 (2.5; 23.4)	.76
Neutrophils	56.5 (39.0; 70.0)	68.0 (45.5; 71.0)	47.5 (32.5; 68.5)	.25
Eosinophils	2.5 (1.0; 8.0)	2.5 (1.5; 10.0)	2.0 (1.0; 4.3)	.26
Steady state				
Maintenance treatment				
ICS dose (fluticasone eq, µg/day)	400 (200; 500)	250 (200; 500)	500 (250; 1000)	.021
LABA	50 (80.6)	31 (77.5)	19 (86.4)	.51
Asthma control (GINA)				
Well-controlled	20 (32.2)	17 (42.5)	3 (13.6)	.006
Partly controlled	25 (40.3)	17 (42.5)	8 (36.4)	
Uncontrolled	17 (27.4)	6 (15.0)	11 (50.0)	
ACT score	22.0 (20.0; 25.0)	23.0 (21.0; 25.0)	20.0 (17.0; 22.0)	<.001
ACT score <20	14 (23.0)	4 (10.3)	10 (45.5)	.002
Lung function				
Pre-β2 agonist FEV1 (% of PV)	81.5 (75.0; 86.0)	83.0 (79.0; 88.0)	75.5 (72.0; 84.0)	.007
Post-β2 agonist FEV1 (% of PV)	88.0 (82.0; 91.0)	89.0 (84.0; 92.0)	85.0 (78.0; 89.0)	.020
FEV1/FVC pré-β2 agonist (%)	96.5 (86.0; 108.0)	100.0 (92.0; 110.0)	88.0 (79.0; 99.0)	.041
FEV1/FVC post-β2 agonist (%)	109.0 (100.0; 115.0)	109.0 (102.0; 114.0)	108.5 (92.0; 119.5)	.79
Virus	21 (35.6)	14 (37.8)	7 (31.8)	.64
Rhinovirus	9 (42.9)	6 (46.2)	3 (37.5)	1.00
Number of cells in sputum (n × 10 ³ /mg)	4.0 (2.3; 14.6)	5.5 (2.4; 19.6)	3.0 (1.5; 6.7)	.17
Neutrophils	25.8 (18.5; 56.0)	26.0 (18.5; 57.5)	25.0 (21.5; 34.0)	.53
Eosinophils	1.0 (0.5; 6.5)	1.0 (0.5; 8.0)	1.0 (0.5; 5.0)	.67
1-year follow-up visit				
Asthma control (GINA)				
Well-controlled	22 (35.5)	18 (45.0)	4 (18.2)	<.001
Partially controlled	27 (43.5)	22 (55.0)	5 (22.7)	
Uncontrolled	13 (21.0)	0	13 (59.1)	

(Continues)

TABLE 1 (Continued)

	Total population n = 62	Good and partial responders (n = 40)	Poor responders (n = 22)	P ^a
≥1 severe exacerbation during the year	22 (35.5)	6 (15.0)	16 (72.7)	<.001
≥2 severe exacerbations during the year	11 (17.7)	0	11 (50.0)	<.001
ACT score	23.0 (21.0; 25.0)	23.0 (21.0; 25.0)	21.5 (17.0; 25.0)	.052
ACT score <20	9 (16.4)	1 (2.9)	8 (40.0)	<.001
Lung function				
Pre-β2 agonist FEV1 (% of PV)	82.0 (75.0; 85.0)	82.0 (78.0; 86.0)	77.5 (70.5; 82.0)	.035
Post-β2 agonist FEV1 (% of PV)	87.0 (79.0; 90.0)	87.0 (81.0; 91.0)	85.0 (76.0; 89.0)	.16
FEV1/FVC pré-β2 agonist (%)	97.0 (85.0; 110.0)	99.0 (89.0; 110.0)	92.0 (80.0; 106.0)	.15
FEV1/FVC post-β2 agonist (%)	106.0 (96.0; 115.0)	107.0 (100.0; 115.0)	102.5 (94.0; 115.0)	.35
Maintenance treatment				
Doses of ICS (fluticasone eq µg/day)	500.0 (250.0; 500.0)	450.0 (225.0; 500.0)	750.0 (250.0; 1000.0)	.026
LABA	51 (82.3)	31 (77.5)	20 (90.9)	.30
Omalizumab	9 (14.5)	1 (2.5)	8 (36.4)	<.001

Note: Values are reported as frequency (percentage) for qualitative variables or median (interquartile range) for continuous variables.

Abbreviations: ACT, Asthma Control Test; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; NA, not applicable.

^aGood/partial responders were compared with poor responders

^b1 missing data.

P-values < .05 were considered statistically significant and appear in bold letters

TABLE 2 Comparison of immune parameters according to 1-year outcomes

	Good and partial responders n = 40	Poor responders n = 22	P
Exacerbation			
Levels in plasma (pg/mL)	n' = 38	n' = 22	
IL-1β	2.0 (2.0; 36.0)	2.0 (1.0; 19.0)	.35
IL-6	2.0 (1.0; 8.0)	10.0 (1.0; 25.0)	.26
IL-5	32.0 (6.0; 92.0)	40.5 (8.0; 64.0)	.59
IL-22	107.0 (29.5; 173.5)	104.0 (52.0; 161.0)	.77
IFN-γ	361.5 (113.0; 679.0)	385.5 (62.0; 1211)	.98
IFN-β	41.0 (23.0; 99.0)	26.5 (20.5; 75.5)	.36
IL-29	639.0 (404.0; 1160)	412.0 (213.0; 954.0)	.27
CCL5	1193 (623.0; 2107)	1374 (872.0; 2212)	.76
Expression of PRR on mDCs (MFI)	n' = 37	n' = 20	
TLR3	32.5 (17.9; 63.9)	23.7 (22.0; 61.1)	.32
RIG-I	59.5 (32.2; 85.9)	63.5 (36.9; 114.0)	.67
Expression of PRR on pDCs (MFI)	n' = 37	n' = 20	
TLR3	36.5 (24.2; 62.1)	39.2 (21.3; 54.0)	.98
RIG-I	59.5 (32.2; 85.9)	67.4 (30.9; 95.0)	.50
Levels in sputum (pg/mL)	n' = 28	n' = 17	
IL-1β	49.0 (12.0; 102.0)	4.0 (2.0; 145.0)	.23
IL-6	20.0 (2.0; 70.0)	21.0 (1.0; 84.0)	.85
IL-5	50.0 (6.0; 215.0)	12.5 (2.0; 112.0)	.32
IL-22	93.0 (5.0; 271.0)	88.5 (5.0; 373.0)	.92
IFN-γ	2.0 (1.0; 61.0)	7.5 (2.0; 41.0)	.56

(Continues)

TABLE 2 (Continued)

	Good and partial responders n = 40	Poor responders n = 22	P
IFN- β	5.0 (5.0; 19.0)	5.0 (5.0; 21.2)	.66
IL-29	5.0 (5.0; 40.5)	7.5 (5.0; 40.0)	.82
CCL5	5.0 (5.0; 153.8)	5.0 (5.0; 131.0)	.92
Steady state (8 wk post-exacerbation)			
Levels in plasma (pg/mL)	n' = 37	n' = 21	
IL-1 β	11.0 (2.0; 88.5)	2.0 (1.0; 19.0)	.19
IL-6	2.0 (2.0; 5.0)	2.0 (1.0; 2.0)	.08
IL-5	36.0 (7.0; 89.0)	30.0 (15.5; 74.0)	0.95
IL-22	105.0 (17.0; 137.0)	151.5 (76.0; 228.5)	.040
IFN- γ	181.0 (47.0; 801.0)	163.0 (80.0; 722.0)	.91
IFN- β	53.0 (19.5; 117.5)	34.6 (9.5; 78.0)	.27
IL-29	803.5 (361.0; 1204)	678.0 (343.0; 1203)	.92
CCL5	1002 (660.0; 1765)	1053 (634.0; 1649)	.58
Expression of PRR on mDCs (MFI)	n' = 37	n' = 20	
TLR3	37.7 (19.5; 56.0)	40.5 (22.9; 57.0)	.82
RIG-I	49.0 (24.0; 80.4)	63.3 (35.0; 75.1)	.36
Expression of PRR on pDCs (MFI)	n' = 37	n' = 20	
TLR3	40.7 (27.6; 58.0)	49.3 (25.5; 68.0)	.45
RIG-I	41.7 (23.3; 70.1)	38.8 (21.2; 57.2)	.69
Levels in sputum (pg/mL)	n' = 16	n' = 8	
IL-1 β	63.0 (2.0; 394.0)	34.0 (2.0; 206.0)	.50
IL-6	2.0 (1.0; 2.0)	1.5 (0.8; 39.0)	.94
IL-5	16.5 (1.0; 34.0)	36.0 (3.0; 279.0)	.33
IL-22	165.0 (8.0; 553.0)	6.5 (5.0; 456.0)	.34
IFN- γ	2.0 (1.5; 9.5)	2.0 (2.0; 87.5)	.51
IFN- β	5.0 (5.0; 21.6)	12.6 (5.0; 24.1)	.78
IL-29	74.0 (11.5; 202.0)	130.0 (10.0; 198.0)	1.00
CCL5	32.1 (5.0; 245.7)	5.0 (5.0; 216.9)	.58

Note: Values are reported as median (interquartile range).

Abbreviations: CCL, C-C motif chemokine ligand; DC, dendritic cell; IFN, interferon; IL, interleukin; MFI, mean fluorescence intensity; PRR, pattern recognition receptors; RIG-I, retinoic acid-inducible gene I; TLR3, Toll-like receptor 3.

P-values < .05 were considered statistically significant and appear in bold letters

This study was approved by the regional investigational review board (Comité de Protection des Personnes Nord Ouest, ref.: 08/07), and parental written informed consents were obtained.

Full characteristics of the population are reported in Table 1. Among the 72 patients (median age = 8.7 years [IQR, 7.6; 11.4]) included at exacerbation, 62 (86%) were followed up and assessed at 1-year visit. More than one severe exacerbation was reported in 22 (36%) and more than two in 11 (18%). At 1-year visit, asthma was partially controlled in 27 (44%) and uncontrolled in 13 (21%); ACT scores were <20 in 14 (23%). Omalizumab was prescribed during the initial exacerbation (inclusion) for one patient who was classified as "partial responder" at 1-year visit. It was initiated in eight patients (15%) during the year of follow-up because of ≥ 2 severe exacerbations and/or uncontrolled asthma despite high doses of maintenance

treatment. These patients were classified accordingly as "poor responders." Finally, 40 patients were classified as "good responders" (16 [26%]) or "partial responders" (24, [39%]) and 22 as "poor responders" (35%) at 1-year visit.

At baseline, allergic comorbidities were not significantly different between poor responders and the others. In poor responders, maintenance treatment at inclusion was more frequently recorded (14 [64%] vs 15 [38%]; $P = .048$) and duration of initial hospitalization was significantly higher. At exacerbation, presence of virus was less frequently detected in poor responders (10 [45%] vs 30 [75%]; $P = .020$); levels of sputum cells, especially eosinophil counts, were not significantly different between the two groups. Regarding immune and inflammatory parameters, blood and sputum levels of IL-1 β , IL-5, IL-6, IL-22, IL-29, IFN- γ , IFN- β , and CCL5 were not

significantly different between poor responders and the others (Table 2). Of note, IL-17A and IL-23 were undetectable in about 70% of patients. Expression of TLR3 and RIG-I on blood myeloid and plasmacytoid DCs was similar.

At steady state, lower levels of pre- $\beta 2$ forced expiratory volume in 1 second (FEV1) and lower levels of pre- and post- $\beta 2$ FEV1/ forced vital capacity (FVC) were recorded in poor responders (Table 1). Cell numbers, eosinophil percentages in sputum, and presence of virus were not significantly different between the groups. Regarding inflammatory response, blood levels of IL-22 were significantly higher in poor responders (Table 2). We observed no difference in other plasma and sputum parameters, including expression of PRRs on DCs.

In the present work, we reported that one quarter of allergic asthmatic children hospitalized for a severe exacerbation presented a subsequent poor response to maintenance treatment during the following year, highlighting the importance of such an event in asthma history. These children may display the features of a difficult, resistant to treatment asthma, conducting in eight out of 22 (36%) of them to omalizumab initiation. Moreover, this subgroup was not particularly sensitive to virus infection and the development of exacerbation was relatively virus-independent. We also observed that control and lung function evaluated 8 weeks after an asthma exacerbation might be predictive of future asthma outcomes.

Poor control and history of exacerbation are known risk factors of future exacerbation.⁹ Fielding et al have recently confirmed the link between altered lung function and poor asthma control and risk of exacerbation.¹⁰ Thus, improving the identification of patients at risk of exacerbations remains an urgent unmet need in childhood asthma.¹¹

To our knowledge, this study is the first to report on the lack of relationship between cytokine profiles in blood and sputum as well as PRR expression in blood DCs at exacerbation and asthma outcomes in the following year. Interestingly, Jackson et al reported no difference in levels of Th1, Th2, and pro-inflammatory cytokines in the bronchoalveolar lavages (BAL) collected during RV16-induced exacerbations in 28 volunteer adult asthmatic patients classified according to asthma control, although uncontrolled patients presented higher virus loads in both nasal fluids and BAL.¹² Considering small sample size, particularly for uncontrolled patients, they could not draw mechanistic conclusions. Of note, we observed higher blood levels of IL-22 at steady state in poor responders. Interleukin-22 is known to promote inappropriate lung tissue remodelling and epithelium activation. Thus, we could hypothesize that these patients might develop a more intense airway remodelling following exacerbation, as reported in severe asthmatic children.¹³ Further studies need to describe the characteristics of tissue remodelling in uncontrolled asthmatic children and might benefit from measuring other immunologic parameters, including levels of alarmins (IL-25, IL-33, TSLP), which play a decisive role in the development of Th2 responses in the airway.⁹

There are a few limitations to our study, including small size and heterogeneity of the population, dosage of a limited and preselected panel of cytokines, assessment of adherence based on parental/ patients' oral reports. Another bias could be the collection of samples at exacerbation after the initiation of systemic corticosteroids. However, this study was conducted in real-life practice and patients were naturally infected by viruses.

In conclusion, we did not observe any relationship between profile of preselected cytokines in blood and sputum at exacerbation and future risk of poor asthma control and/or recurrence of exacerbations at 1 year in a cohort of allergic asthmatic children. Notably, we observed higher levels of IL-22 at steady state in poor responders, possibly reflecting a higher degree of airway remodeling. Improving our understanding of the pathophysiological mechanisms leading to asthma outcomes following a severe exacerbation is urgently needed in order to improve treatment strategy, especially in severe asthmatic patients.

KEYWORDS

asthma, exacerbation, innate immunity, outcomes, virus

ACKNOWLEDGEMENTS

The authors would like to thank the patients and their families who participated in the study, all the nurses, chest physiotherapists, laboratory technicians, and doctors who participated in the enrolment, sampling, and follow-up of patients, in particular Dr Patrick GELE (CRB-CIC-1403-INSERM-CHU) for biological sample storage management and traceability, Mrs Eva VILAIN and Gwenola KERVOAZE (CIIL, INSERM U1019) for their excellent technical assistance. We also thank H  l  ne Bauderlique for her help and advice on flow cytometry (BICel Cytometry Platform, Institut Pasteur de Lille, France).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Stéphanie Lejeune^{1,2} Clémence Mordacq^{1,2}Elodie Drumez³

Sarah Brisset¹

Guillaume Pouessel^{1,4} Muriel Pichavant² Ilka Engelmann⁵Laurent Béghin⁶ Irina Decleyre-Badiu^{1,7}Véronique Neve⁷

Caroline Thumerelle^{1,2}

Philippe Gosset² Antoine Deschildre^{1,2}

¹Pediatric Pulmonology and Allergy Department, CHU Lille, Hôpital Jeanne de Flandre, Univ. Lille, Lille cedex, France

²Center for Infection and Immunity of Lille, INSERM Unit, CNRS UMR 8204, Institut Pasteur de Lille, Univ. Lille, Lille cedex, France

³Department of Biostatistics, EA 2694 - Santé Publique: Épidémiologie et Qualité Des Soins, CHU Lille, Univ. Lille, Lille, France

⁴Pediatric Department, CH Roubaix V, Roubaix cedex, France

⁵Virology Laboratory, Institute of Microbiology, CHU Lille, Univ. Lille, Lille cedex, France

⁶Clinical Investigation Center, LIRIC UMR 995 Inserm, CIC-1403-Inserm-CHU, CHU Lille, Univ. Lille, Lille, France

⁷Pulmonary Function Testing Department, CHU Lille, Univ. Lille, Lille, France

Correspondence

Antoine Deschildre, Pediatric Pulmonology and Allergy Department, CHU Lille, Hôpital Jeanne de Flandre, Univ. Lille, 59037 Lille cedex, France.
Email: antoine.deschildre@chru-lille.fr

ORCID

Stéphanie Lejeune  <https://orcid.org/0000-0001-7009-2113>

Elodie Drumez  <https://orcid.org/0000-0003-4103-236X>

Guillaume Pouessel  <https://orcid.org/0000-0003-4118-6385>

Muriel Pichavant  <https://orcid.org/0000-0002-1315-4397>

Laurent Béghin  <https://orcid.org/0000-0001-5369-3910>

Philippe Gosset  <https://orcid.org/0000-0002-4043-6429>

Antoine Deschildre  <https://orcid.org/0000-0003-2006-7221>

REFERENCES

1. Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax*. 2018;73:313-320.
2. Engelmann I, Mordacq C, Gosset P, et al. Rhinovirus and asthma: reinfection, not persistence. *Am J Respir Crit Care Med*. 2013;188:1165-1167.
3. Subrata LS, Bizzintino J, Mamessier E, et al. Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children. *J Immunol*. 2009;183:2793-2800.
4. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med*. 2005;201:937-947.
5. Edwards MR, Regamey N, Vareille M, et al. Impaired innate interferon induction in severe therapy resistant atopic asthmatic children. *Mucosal Immunol*. 2013;6:797-806.
6. Sykes A, Edwards MR, Macintyre J, et al. TLR3, TLR4 and TLRs7-9 induced interferons are not impaired in airway and blood cells in well controlled asthma. *PLoS ONE*. 2013;8:e65921.
7. Deschildre A, Pichavant M, Engelmann I, et al. Virus-triggered exacerbation in allergic asthmatic children: neutrophilic airway inflammation and alteration of virus sensors characterize a subgroup of patients. *Respir Res*. 2017;18:191.
8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. www.ginasthma.org
9. Edwards MR, Strong K, Cameron A, Walton RP, Jackson DJ, Johnston SL. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. *J Allergy Clin Immunol*. 2017;140:909-920.
10. Fielding S, Pijnenburg M, de Jongste JC, et al. Change in FEV1 and feno measurements as predictors of future asthma outcomes in children. *Chest*. 2019;155:331-341.
11. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet*. 2018;391:350-400.
12. Jackson DJ, Trujillo-Torralbo MB, del-Rosario J, et al. The influence of asthma control on the severity of virus-induced asthma exacerbations. *J Allergy Clin Immunol*. 2015;136:497-500.
13. Chang Y, Al-Alwan L, Risse PA, et al. Th17-associated cytokines promote human airway smooth muscle cell proliferation. *FASEB J*. 2012;26:5152-5160.