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Factors associated with asthma exacerbations in schoolchildren: an experience in clinical practice

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To the Editor,

chronic airway inflammation is the primary pathophysiological feature in patients with asthma (1). The type-2 phenotype is most common in childhood (2). Consistently, children with type-2 phenotype have frequently respiratory infections as type-2 immune response is characterized by a defective defense against pathogens (3). This aspect has a clinically relevant consequence as acute respiratory infections usually precede asthma exacerbations, mainly in children (4).

Asthma exacerbation is an acute or sub-acute episode of airflow obstruction occurring on a background of chronic airway inflammation and bronchial hyperresponsiveness (5). Bronchoconstriction and increased mucus production characterize asthma exacerbation. As a result, asthma symptoms, including wheeze, cough, dyspnea, and respiratory distress, worsen during asthma exacerbation (6). The exacerbation outcomes usually include the need for systemic corticosteroids, urgent unscheduled care, emergency department or urgent care visits, and hospitalizations for asthma (7). Asthma exacerbations, therefore, represent a demanding challenge in daily practice. As a result, a thorough workup should identify factors associated with asthma exacerbations.

Here, we would propose our experience conducted on a sample of schoolchildren with asthma and followed at the level of primary care pediatrics. The research aimed to investigate possible factors associated with asthma exacerbation in a defined narrow time frame, *i.e.*, the fall/winter season.

The inclusion criteria were: age between 6 to 14 years, and asthma diagnosis, according to GINA criteria (1). The exclusion criteria were: previous or current allergen immunotherapy, congenital or acquired immunodeficiency, cystic fibrosis, and chronic pulmonary diseases.

All the children with asthma exacerbation were evaluated by one of the participant investigators.

Clinical characteristics included demographic data, family atopy, smoking habitude, history of asthma exacerbations, allergies (documented by sensitization), and current treatment.

Children were considered allergic if symptoms occurred after exposure to the sensitizing allergen (8). Sensitization was defined as presence of allergen-specific IgE, documented by skin prick test (a wheal 3 mm or larger than the negative control was considered positive; the extracts were manufactured by Lofarma, Milan, Italy). The list of tested allergen extracts included: grasses, pellitory wall, ragweed, birch, hazelnut tree, olive tree, cypress, house dust mites, dog, cat, *Aspergillus fumigatus,* and *Alternaria alternata.*

The Ethics Committee of the ASL Naples 2 approved the study. In addition, written informed consent was obtained from all parents.

The statistical analysis consisted of the independent samples t-test or non-parametric Mann-Whitney test to compare continuous variables between groups (no exacerbation episode *vs* at least one episode).

Table I *- Factors associated with the occurrence of at least one asthma exacerbation.*

	Total (n = 139)	**No asthma exacerbation (n = 107)**	**With asthma exacerbation (n = 32)**	**Univariate P-value**	**Multivariate OR (95%CI); P-value**
Age	8.4 ± 2.72	8.6 ± 2.79	7.5 ± 2.30	0.020*	
Sex					
Female	60 (43.2%)	50 (46.7%)	10 (31.3%)	0.12	
Male	79 (56.8%)	57 (53.3%)	22 (68.8%)		
Living					
City	94 (67.6%)	70 (65.4%)	24 (75.0%)	0.31	
Countryside	45 (32.4%)	37 (34.6%)	8 (25.0%)		
Passive smoking					
None	80 (57.6%)	61 (57.0%)	19 (59.4%)	0.81 (none *vs* any smoker)	
Father	25 (18.0%)	21 (19.6%)	4 (12.5%)		
Mother	9 (6.5%)	7 (6.5%)	2 (6.3%)		
Both parents	22 (15.8%)	16 (15.0%)	6 (18.8%)		
Other cohabitants	3 (2.2%)	2 (1.9%)	1 (3.1%)		
Family atopy					
No	40 (28.8%)	30 (28.0%)	10 (31.3%)	0.73	
Yes	99 (71.2%)	77 (72.0%)	22 (68.8%)		
Number of asthma exacerbations in the past	5.8 ± 4.32	5.3 ± 3.28	7.4 ± 6.5	0.044*	OR 1.11 (1.01-1.24); 0.048
Allergy					
No allergy	68 (48.9%)	51 (47.7%)	17 (53.1%)	0.86	
Mono-allergy	39 (28.1%)	31 (29.0%)	8 (25.0%)		
Poly-allergy	32 (23.0%)	25 (23.4%)	7 (21.9%)		
Pet allergy	5 (3.6%)	3 (2.8%)	2 (6.3%)	0.33	
HDM allergy	52 (38.8%)	42 (40.4%)	10 (33.3%)	0.49	
Pollen allergy	14 (10.1%)	11 (10.3%)	3 (9.4%)	0.88	
Background treatment					
No medication	52 (37.4%)	39 (36.4%)	13 (40.6%)	0.64	
SABA alone as needed	28 (20.1%)	22 (20.6%)	6 (18.8%)		
Low-dose ICS	23 (16.5%)	16 (15.0%)	7 (21.9%)		
Medium-dose ICS	36 (25.9%)	30 (28.0%)	6 (18.8%)		

In addition, the chi-square test or Fisher's exact test evaluated the association between categorical variables. Subsequent modeling (univariate and multivariate) was performed using stepwise selection with the significance level for retention in the model set at $\alpha \leq 0.10$.

Results were quantified by odds ratio (OR) and a 95% confidence level (95%CI). The significance level was set at 0.05. The analyses were computed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

The characteristics of the schoolchildren are reported in **table I**. Comprehensively, 139 children were evaluated. The mean age was 8.4 years; the male gender was prevalent (56.8%), and passive smoking was declared in 42.4% of families. Family atopy was common (71.2%). The mean number of asthma exacerbations in the past was 5.8. About half (51.1%) of children were allergic (mainly with a single allergy). House dust mite (HDM) allergy was prevalent. About one-third of children did not take any medication, about 40% took inhaled corticosteroids, and 20% bronchodilators alone.

The study analysis stratified children into two subgroups: children without asthma exacerbation during the observation period and children with at least one asthma exacerbation. Children with at least one asthma exacerbation were older than those without asthma. In addition, children with asthma exacerbation had more exacerbation episodes in the past than children without exacerbation. The multivariate analysis demonstrated that the number of previous asthma exacerbations was associated with current asthma exacerbation (OR 1.11).

However, second-hand smoke, allergy, and type of medications were not associated with asthma exacerbation occurrence.

Asthma exacerbations represent an important issue in pediatric clinical practice (9). In childhood, the acute upper airway infections, mainly of viral origin, represent the leading cause of asthma attacks requiring medical aid (10). Viral infections implicate bronchial inflammation that triggers airway hyperresponsiveness and further narrows the bronchial lumen (11). These phenomena depend on the overexpression of type-2 immune response usually involved in pediatric asthma.

In addition, asthma exacerbations, mainly if associated with hospitalization, create a burden for the healthcare system and negatively affect children and their families. Frequent exacerbations are also associated with asthma worsening, including function (12).

The present report had some limitations, including the short observation period, the lack of biomarkers assessment, and the documentation of infections origin. However, the clinical relevance resides in its being conducted in a real-life pediatric primary care setting.

It is clinically relevant to highlight the importance of an adequate and thorough workup in managing children with asthma exacerbation. In addition, this observation underlined the relevance of the number of previous exacerbations. Finally, it implies the need to consider adequate preventive measures to adopt, such as vaccinations, anti-inflammatory agents, allergen-specific immunotherapy, if indicated, and potentially, as recently reported, immunomodulation (13).

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GC: conceptualization, writing - original draft. MG, IS: data curation. MMdG, MAT: writing - review editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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