The treatment of allergic rhinitis in asthmatic children and adolescents: practical outcomes from the real-world "ControL'Asma" study.

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To the Editor,

Allergic rhinitis (AR) affects up to 40% of children and adolescents (1). AR is characterized by a type 2 inflammation, including allergen-specific IgE production, eosinophilic infiltrate, and T helper 2(Th2)-derived cytokines (2). T regulatory cells' specific and functional defect promotes the typical Th2 polarization in allergic patients (2). Asthma is the most common chronic disease of childhood and adolescence (3). Asthma management is, therefore, a daily challenge in pediatric practice (4). Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation (3). To define clinical, functional, and immunopathological patterns allows identifying asthma phenotypes and endotypes (5). In this regard, the allergic asthma phenotype is the most common in childhood and is defined when asthma symptoms and airway eosinophilic inflammation are associated with inhalation of the sensitizing allergen (3). There is also a close link between eosinophilic airway inflammation and airflow limitation (6). Therefore, AR and asthma share common pathogenic mechanisms and are frequently associated (7). In clinical practice, the concomitant treatment of asthma and AR can commonly produce practical problems. The relief of symptoms and control of airway inflammation represents the cornerstone of their management, even though some exceptions (3,8). Symptoms relief need bronchodilator use in asthma and essentially antihistamines (anti-H1) in AR, but inflammation resolution depends on inhaled corticosteroids (ICS) in asthma and intranasal corticosteroids in AR. However, the overtreatment of both diseases may generate adverse events, mainly concerning corticosteroids that may induce relevant issues (9). Allergen immunotherapy (AIT) could represent the shared treatment committed to restoring allergen tolerance, revert Th2 polarization, and ultimately dampen type 2 inflammation (10).

The Italian Society of Pediatric Allergy and Immunology recently established a prospective study ("Control Asma") to investigate the asthma control in children and adolescents managed in clinical practice. This research has been paid attention to the concomitant treatment of AR in children and adolescents with asthma. This cross-sectional study included a series of asthmatic children and

adolescents consecutively visited across 10 Italian Pediatric Allergy centers. The centers are in Genoa, Bergamo, Milan, Pavia, Parma, Pisa, Rome (3 centers), and Catanzaro. All patients were currently treated according to the GINA guidelines based on the asthma control level and AR guidelines (11). The visit included careful history, mainly concerning asthma duration, current use of asthma and AR medications, including inhaled corticosteroids dosage (ICS) expressed as beclomethasone equivalence, oral corticosteroids use, rhinitis and allergy comorbidity, clinical examination, lung function testing (including bronchodilation testing), asthma control level according to the GINA guidelines (3). The Ethics Committee initially approved the procedure of the Istituto Giannina Gaslini of Genoa (code number: 22253/2017; in the Italian Project "ControL'Asma" promoted by the Italian Society of Pediatric Allergy and Immunology). All the other Review Ethics Committees further approved the study procedure, and written informed consent was obtained from all parents. Clinical data were recorded by an electronic case report form designed expressly for this study. Descriptive statistics of the study patients were firstly calculated; qualitative data were reported in terms of absolute frequencies and percentages; quantitative data were reported in terms of medians, first and third quartiles (1st – 3rd q).

The normality of distributions was evaluated using the Shapiro-Wilk test.

The statistical software "Statistica" (version 9, StatSoft Corporation, Tulsa, OK, USA) was used for all the analysis, and the software "Stata" (version 11, Stata Corporation, College Station, TX, USA) was used to calculate the Shapiro-Wilk.

Globally, 480 subjects were enrolled; 423 (88.1%) had AR comorbidity. Table 1 reports the clinical characteristics of the patients with both diseases. Signally, there was a male predominance (70%); well-controlled asthma was 55%, moderate-severe AR in 14%. ICS were used in 75% and OCS in 23%, and antileukotrienes in 24%. Antihistamines were used in 57.6%, intranasal corticosteroids in 53%, and both combined in 35. Notably, about ¾ of patients used pharmacotherapy for AR, only 19.5%, in contrast, used AIT. As regards sensitization, house dust mites were the most common sensitizing allergen (78%), followed by grasses (60%), olive tree (36%), cat (31%), hazelnut tree

(25%), birch (23.4%), dog (21%), Alternaria (20%), cypress (16%), *Parietaria* (16%), and *Compositae* (15%). There were geographical differences concerning the distribution of specific sensitizations consistently with previous studies (12-14). Nevertheless, there was no significant difference in terms of treatments and disease severity among the centers. It mainly depended on the uniform sharing to International guidelines for asthma and rhinitis and the fact that all centers were third-level pediatric allergy clinics.

The current study demonstrated that AR is prevalent comorbidity in children and adolescents with asthma as affected by almost 90% of the whole sample. This outcome underlined the clinical relevance of the concept of united airways disease (15). However, corticosteroids were the most common medication as ICS was used in nearly all subjects and intranasal corticosteroids in more than half. However, antihistamines (mostly oral) were the first-choice treatment for AR.

These findings arouse some concern concerning potential adverse events related to medication use. On the other hand, AIT was used only in 20% of patients. It is well known that medications do not cure the allergy, as symptoms and inflammation quickly recur after their suspension (16,17). AIT should represent the choice treatment of AR and allergic asthma as restores immunological and clinical tolerance toward the causal allergen, may prevent allergy worsening, and its effects are longlasting over time. Also, there is a predominance of sensitization to perennial allergens, such as it means that allergic inflammation persists throughout the year. Anti-inflammatory medications should be used for a long time, with the problem of side effects. As a result, a more rational approach should be pursued in asthmatic children and adolescents.

The current study had some limitations, mainly concerning the cross-sectional design and the lack of biomarkers assessment. However, a follow-up study is ongoing. Moreover, the strength of this study was the nationwide size that provides generalizability of the outcomes. This real-world study may also provide information more adherent to the daily practice that studies involving selected patient populations that rarely mirror the real situation (18).

In conclusion, the present study demonstrated that AR was common asthma comorbidity in children and adolescents. Well-controlled asthma affected only half of the patients despite the use of corticosteroids was widespread and perennial allergy was also predominant. AIT was scarcely prescribed. These outcomes have to convince that more efforts should be made to improve asthma management in children and adolescents.

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Table I. *Description of the study patients with allergic asthma and rhinitis.* * median values and 1st and 3rd quartiles.

Clinical characteristics		**Sensitization to**	
Age (years)	11.4 [9.4 - 13.8] *	House dust mites	76 %
Males	69.3 %	Grasses	59.7%
Females	30.7 %	Olive tree	35.8 %
Well-controlled asthma	54.9 %	Cat	30.6 %
Partly controlled asthma	32.5 %	Hazelnut tree	24.7 %
Uncontrolled asthma	12.6 %	Birch	23.4%
Mild intermittent AR	37.9 %	Dog	20.7 %
Moderate/severe intermittent AR	9.2 %	*Alternaria*	19.6 %
Mild persistent AR	47.6 %	Cypress	16.4 %
Moderate/severe persistent AR	5.2 %	*Parietaria*	16.3 %
ICS low dose	41 %	*Compositae*	14.9 %
ICS medium dose	32.1 %		
ICS high dose	3.1 %		
OCS: at least 1 course/year	22.7 %		
LABA	35.5 %		
Anti-LTC	24.3 %		
Intranasal corticosteroids	53 %		
Anti-H_1	57.6 %		
Intranasal corticosteroids + Anti-H_1	35.0 %		
Allergen-specific Immunotherapy	19.5 %		