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Pollen-induced asthma: a unique model of mild to moderate asthma

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Asthma is a disease that affects approximately 300 million people worldwide (1), and patients with mild asthma represent approximately 50-75% of this population (2).

Although patients with mild asthma constitute the vast majority of asthmatics, it is a subgroup still understudied and mistakenly considered to be easy to manage clinically. In fact, the so-called mild asthma remains a poorly researched clinical area despite its significant impact on the life of some patients, particularly because of the possibility of experiencing severe exacerbations (3).

The definition of mild asthma itself is not consistently agreed upon by the main guidelines, and this lies in the assumption that the level of severity and frequency of symptoms is stable over time, and in the attempt to standardize the different characteristics of all patients under a single umbrella diagnosis (4).

Instead, it has been emphasized recently that the so-called mild asthma is in fact a heterogeneous condition characterized by different pathogenic and inflammatory mechanisms and clinical manifestations which may benefit from a differentiated and personalized management approach (5).

From this perspective, the works by Cecchi *et al.* on pollen-induced asthma (PIA) (6, 7), which has previously been classified as one of the clinical manifestations of mild-moderate asthma due to its long asymptomatic or paucisymptomatic periods, suggest that PIA might be considered as specific phenotype of asthma.

Early phenotyping, even in non-severe asthma, has recently been highlighted as a useful tool to improve a "precision" approach to asthma therapy (8). PIA meets the criteria for defining a phenotype as outlined by Han *et al.* (9). An ongoing issue in defining phenotypes is ensuring their long-term stability and addressing potential overlaps or transitional features with other phenotypes. However, several reviews and cohort studies indicate that this phenotype generally remains stable in the long-term (10, 11). The definition of PIA as a phenotype paves the way for a specific diagnostic algorithm, where T2 biomarkers, particularly FeNO, but also eosinophils, play a significant role as they can be considered endotypic diagnostic tests for PIA (6). The paper of Cecchi *et al.* also highlights how the diagnosis of PIA can be difficult outside the exposure period (6). In fact, the low expression of T2 markers and the low level of inflammation minimize the instability of the airway caliber and therefore the variability of FEV1, the positivity of the bronchodilation test and also the airways hyperreactivity, which are markers common to all asthma phenotypes (12).

The interpretation of PIA as a phenotype has important implications from a management point of view. The paper of Cecchi *et al.*, in fact, underlines how in these subjects the use of ACT as well as the use of cut-off values for the frequency of symptoms usually used to evaluate the "control domain" can be falsely reassuring when assessed outside the exposure periods and therefore lead to an underestimation of the patient's possible therapeutic needs during periods of maximum pollen exposure (6). The authors (6, 7) therefore suggest the adoption of a multidimensional "risk prediction" score that includes clinical history, symptoms, respiratory function, biomarkers, and comorbidities, in order to assess, even if indirectly, the patient's actual future risk and to personalize the therapeutic strategy.

Severe exacerbations and near-fatal asthma or fatal asthma episodes cannot be predicted in an individual subject because they are the result of a number of risk factors that add up and are potentiated in a variable way depending on the circumstances. However,

they can be preventable through the adoption of specific clinical tools such as an accurate risk stratification and the adoption of the maximum precautionary principle, which aims to adopt the more appropriate therapeutic approach (6, 7).

Therefore, adopting a proactive therapeutic strategy, when indicated, and a rapid step-up during the exposure season represents an advantageous strategy at a time when the patient is particularly vulnerable and when the transition from the onset of symptoms to a flare-up can be extremely rapid.

The aim of minimizing and preventing symptoms by adopting a proactive and non-reactive approach offers the additional advantage of avoiding phenomena of repeated instability of the caliber of the airways. Repeated bronchoconstriction episodes associated with allergic exposure favours crosstalk between the epithelium, inflammatory cells (eosinophils and mast cells) and smooth muscle cells which determines the activation and persistence of a T2 type inflammation and bronchial remodelling phenomena (12, 13).

From a clinical point of view, pharmacodynamic and pharmacokinetic characteristics of the inhaled corticosteroid should maximize bronchoprotection (14), thus effectively attenuating the airways hyperreactivity, which represents an important factor that influences the subjective threshold for allergen-induced bronchoconstriction (8).

In conclusion, the works by Cecchi *et al.* (6, 7) provide us with a new management strategy for PIA and offer us indications on how to look beyond the appearances and to recognize in time the "slumbering fire" and to adopt the most appropriate therapeutic strategy to control asthma during the pollen exposure season and avoid severe exacerbations.

This new interpretation of PIA allows us to overcome the simplistic indication of a "one-size-fits-all therapy" and to initiate a "precision" approach based on a careful and individual stratification of "future risk".

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