POSITION PAPER
Eur Ann Allergy Clin Immunol Vol 57, N.5, 211-227, 2025

Lorenzo Cecchi[1], Antonino Musarra[2,*], Kliljeda Jaubashi[3], Alessandro Maria Marra[4], Matteo Martini[5,6], Francesco Papia[7], Giuseppe Valenti[7], Baoran Yang[8], Adriano Vaghi[9,**], Maria Beatrice Bilò[5,6]

Pollen-induced asthma: diagnostic and therapeutic implications

[1]Allergy and Immunology Unit, San Giovanni di Dio Hospital, USL Toscana Centro, Florence, Italy
[2]Allergy Unit, Casa della Salute di Scilla, Scilla, Reggio Calabria, Italy
[3]Pulmonology Unit, ASST Santi Paolo Carlo, Milan, Italy
[4]Pulmonology Unit, ASST Rhodense, Garbagnate Milanese Hospital, Milan, Italy
[5]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Italy
[6]Allergy Unit, Department of Internal Medicine, University Hospital delle Marche, Ancona, Italy
[7]Allergology and Pulmonology Unit, Provincial Outpatient Center of Palermo, Palermo, Italy
[8]Allergy Clinical Immunology and Rheumatology Unit, ASST Carlo Poma, Mantua, Italy
[9]Former Head of Pneumology and Chief of the Department of Medicine and Rehabilitation, Guido Salvini Hospital-ASST Rhodense, Garbagnate Milanese, Milan, Italy
[*]Joint first co-authorship
[**]Joint senior co-authorship

Key words

Pollen-induced asthma; phenotype; asthma treatment; asthma diagnosis.

Corresponding author
Matteo Martini
Allergy Unit
Department of Internal Medicine
University Hospital delle Marche;
Department of Clinical and Molecular Sciences
Marche Polytechnic University
via Conca 71
60126 Ancona, Italy
ORCID: 0000-0001-9873-9695
E-mail: matteo.martini.med@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.408

Summary

Evidence supports the hypothesis of pollen-induced asthma as a specific asthma phenotype, with defined clinical features and tailored pathways for its clinical management.
The probability of diagnosis varies significantly in the pollen season, in which allergic patients are symptomatic, as compared to asymptomatic periods outside the pollen season. In this context, a novel diagnostic scheme for pollen-induced asthma has been developed.
Pollen exposure is the key risk factor for symptoms and exacerbations. Therefore, we proposed a therapeutic algorithm for pollen-induced asthma based on a risk stratification model that considers the medical history of the patients and the measurement of objective markers, allowing a tailored therapeutic approach.

Impact statement

Pollen-induced asthma can be considered a specific asthma phenotype, with defined clinical features and tailored diagnostic and therapeutic pathways for its clinical management.

Introduction

Pollen-induced asthma (PIA) could be considered a specific phenotype. As reported by Cecchi *et al.* (1), pollen allergenicity depends not only on genetic and environmental factors, but also on immunostimulatory components of the pollen matrix, that contribute to airway disease and may represent a defining feature of allergic asthma.

A phenotype is commonly defined as "*the visible characteristics of an organism resulting from the interactions between its genetic* *patrimony and the environment*". In this article, we will adopt an operational description, useful from a clinical point of view. Therefore, by asthma phenotype we mean *"the characteristics of the disease, single or in combination, which describe the difference between individuals affected by the same disease, and which are correlated with clinical outcomes: clinical history and symptoms (onset, duration, control of symptoms, exacerbations), impaired respiratory function, disease progression, biomarkers, comorbidities and response to the treatment*". Thus, the identification of specific phenotypes should have a predictive value in terms of clinical outcomes and response to therapy (2-4).

The Global Initiative for Asthma (GINA) document highlights the importance of phenotyping in severe asthma for the purpose of indicating biological drugs, while, although the definition recognizes that asthma is a heterogeneous disease, the identification of the phenotypes of mild-moderate asthma is not considered relevant because the therapeutic approach recommended in these patients is in any case independent of the phenotypes (5).

Evidence supporting PIA as a specific phenotype can be derived using both a down-type investigation methodology (expert clinical judgement) and an unsupervised one (button up, cluster analysis):

- Pollen-induced asthma as a clinical phenotype: respiratory symptoms, exacerbations, impaired respiratory function, and increase in T2 biomarkers are all elements that are quantitatively linked to the seasonal exposure to pollen to which the patient is sensitized, while in the remaining period of year the patient remains asymptomatic (1). The strategy for evaluating asthma control, in particular the risk of exacerbations and clinical worsening, is strongly influenced by exposure to allergens. Similar to the severe asthma phenotypes, for PIA a targeted therapy is available, represented by specific immunotherapy, as well as a mainly seasonal symptomatic and anti-inflammatory pharmacological therapy.
- Pollen-induced asthma phenotype identified with cluster analysis: three large cohort studies using different clustering techniques to describe possible asthma phenotypes (SARP, U-BIOPRED, UK cohort), identified a cluster characterized by mild allergic asthma (cluster 1 in the SARP cohort and cluster 3 in the U-BIOPRED cohort), with characteristics compatible with those above described as PIA (6-8). Despite the difference between the studies, Kaur *et al.* (3) identified 4 phenotypes: 1) early onset mild allergic asthma; 2) early onset moderate-severe allergic asthma; 3) late onset non-allergic eosinophilic asthma; 4) late onset non-allergic non-eosinophilic asthma. The main factors discriminating the heterogeneity of asthma common to the different phenotypes are the age of onset, respiratory function, atopy and eosinophils. Other patient characteristics, such as sex, obesity and smoking, although commonly detected, play a less important role when comparing studies.

Altogether, the identification of PIA as a clinical phenotype has a predictive value in terms of clinical outcomes and response to therapy (4). According to Han *et al.* (4), it is possible to identify a clinical phenotype when subjects are characterized by similar clinical presentations (respiratory symptoms occurring during the period of exposure to pollen), pathogenic mechanisms, diagnostic pathways, biomarkers, and availability of an endotype-specific therapy (disease modifying such as immunotherapy).

Materials and methods

A narrative systematic review of the literature was conducted on Medline to identify English papers published up to March 31, 2024. Hand searching of references of interest was also performed within the selected studies. The search strategy included papers with the terms "asthma" and "pollen/allergic" asthma in title/abstract, associated with at least one keyword, in the title/abstract, for each of the following domains: adherence to medications, risk of exacerbations, diagnosis, and treatment.

The research and selection of the studies were performed independently by five allergists, who collected and summarized the data from the studies. All the authors contributed to the definition of the research questions and related keywords, and to the final selection of the studies to be included in the systematic review. Considering the paucity of data about PIA and the low-quality evidence of the obtained studies, a formal process to assess the certainty in the body of evidence or the strength of the recommendations was not performed. Consensus was sought from a panel of asthma experts from the Asthma Interest Group of AAIITO (Association of Italian Hospital Allergists and Immunologists), with a formal voting process implemented in case of disagreement during the discussion. The final consensus paper was reviewed and approved by all the authors.

Pollen-induced asthma: diagnostic flow chart

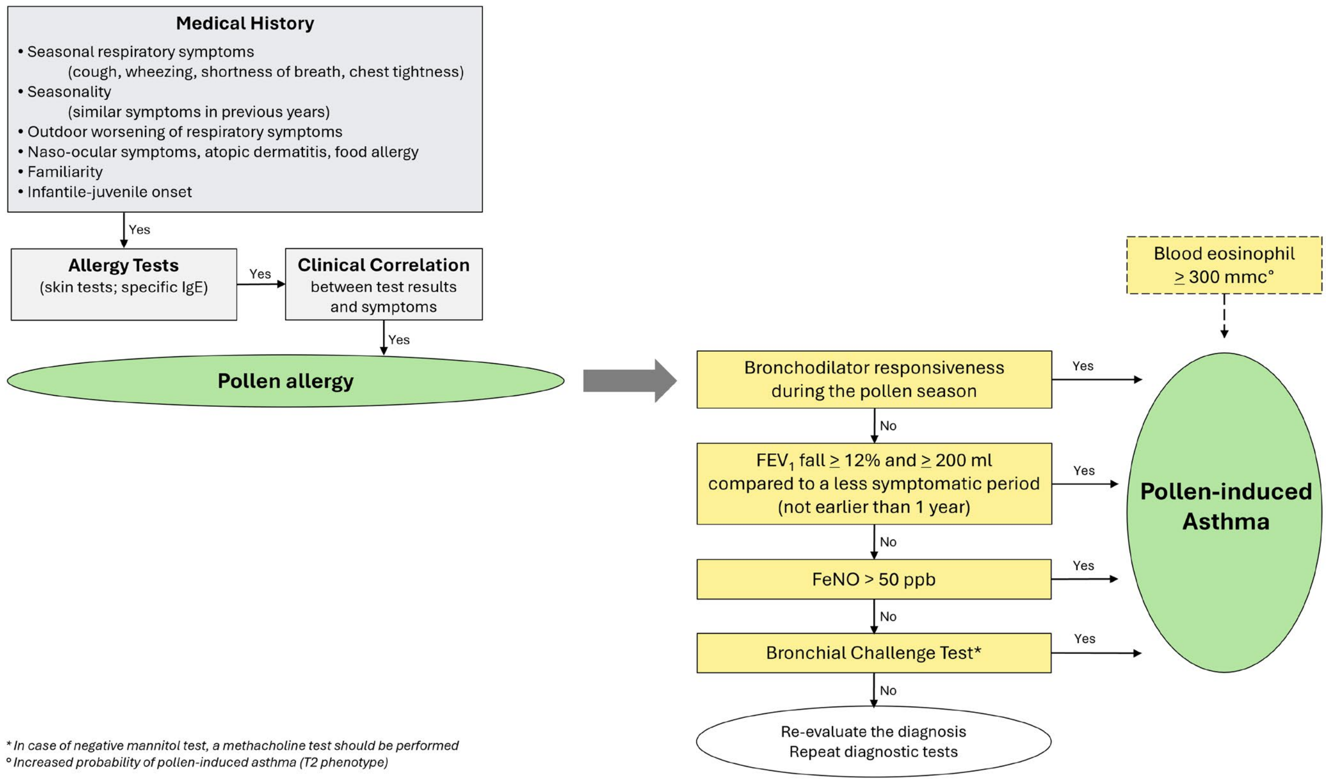
Allergic asthma is the most common asthma phenotype, characterized by early onset, immunoglobulin type E (IgE) sensitization to allergens, IgE-related Th2-mediated background (9).

Allergic rhinitis is a common comorbidity of asthma and, in the case of PIA, is observed in the vast majority of patients, over 80% (10).

Usually, the diagnosis of PIA is suspected during the symptomatic period of exposure to the pollen to which patients are sensitized. The proposed diagnostic path for PIA is summarized in the flow chart (**figure 1**).

The process starts from the medical history, that may suggest the presence of a pollen-induced respiratory disease, followed by allergy tests and assessment of the compatibility between the seasonality of symptoms and the positivity towards the identified allergens. In fact, the presence of a positive skin test or positive sIgE does not necessarily mean that the allergen is causing symptoms and

Figure 1 *- Pollen-induced asthma diagnosis.*



there is still no evidence regarding sIgE thresholds necessary to confirm or exclude clinical disease (5, 11). The clinical relevance of sensitization needs to be confirmed by patient's history (5, 11). A recent diagnostic technique, known as "component resolved diagnostics" (CRD) is used to determine the specific molecules (or components) against which the IgE have been produced, to distinguish between genuine sensitization and clinically irrelevant IgE cross-reactivity due to panallergens or carbohydrate determinants (12-14), and to guide the choice of allergen specific immunotherapy (AIT).

In the case of symptoms suggestive of asthma (cough, wheezing, chest tightness, shortness of breath, nocturnal awakenings for asthma) along with seasonal onset (*i.e.*, temporal association between symptoms and pollen exposure), a pollen-induced variability in expiratory lung function must be also documented to confirm the diagnosis of PIA. The first line recommended test is spirometry showing a decrease of ≥ 12% and ≥ 200 ml compared to a previous test carried out in a less symptomatic period but not earlier than one year (5, 15). This diagnostic process can be carried out in any clinic where a spirometer is available, even a portable one; the only limiting factor is the correct technical execution of the test. A bronchodilation test with SABA during pollen exposure is recommended, as a ≥ 12% and ≥ 200 ml increase in FEV1 confirms the diagnosis of PIA. It was not considered appropriate to establish the finding of obstructive spirometry, with FEV1/FVC < the lower limit of normal (LLN) or < 75% (5, 15-17), as a pre-condition for carrying out the bronchodilation test, as the patients with PIA frequently show non-obstructive spirometry, especially when the prevalent symptom is cough. On the other hand, the fact that in these patients the respiratory parameters are frequently normal reduces the probability of a positive bronchodilation test, thereby limiting the sensitivity of the test, even if the specificity is good.

A negative bronchodilation test does not exclude a diagnosis of PIA: in this case it is suggested to perform a direct (methacholine) or indirect (mannitol) bronchial challenge during the pollen exposure, if the FEV1 change from extra-pollen period to pollen period is inconclusive.

A positive result with mannitol (PD15 < 635 mg) is indicative of a high degree of bronchial inflammation, but this test is less sensitive, although more specific, than the test with methacholine using a cut-off value of PC20 < 8 mg/ ml (18-20). It will be the doctor's choice to carry out the test with mannitol first, being more informative regarding the activity of the inflammatory processes and easier in the execution. In the event of a negative result with the mannitol test, a test with methacholine should be performed (18). If even in this case the result is negative, the diagnosis of asthma can be excluded or, if the suspicion of asthma remains, the test can be repeated in a more symptomatic period (18). It is important to underline that in PIA, airway hyperresponsiveness (AHR) increases and can have clinically diagnostic value only during the pollen exposure (21, 22).

GINA report suggests lung function testing with the handled device peak expiratory flow (PEF) meter, when spirometry is not available, to assess excessive variability in expiratory lung function (5). Although PEF is less reliable than spirometry parameters, it is better than relying on symptoms alone.

The assessment of T2 inflammation should always be included in the diagnostic work-up for PIA, using appropriate biomarkers. Therefore, FeNO testing should be also performed, being a surrogate measure of eosinophilic lung inflammation, which could persist even in the absence of overt respiratory symptoms (23, 24). This test is recommended if spirometry is not available: the guidelines from the British Thoracic Society, the National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network (BTS/NICE/SIGN), and from the European Respiratory Society (ERS) suggest FeNO measurement as a part of the diagnostic work-up in adult patients with suspected asthma, in whom the diagnosis is not established based by initial spirometry combined with bronchodilator responsiveness testing (15, 16). Values > 50 ppb are considered diagnostic for asthma (16, 25). This cut off is higher than the one previously recommended in the previous edition of NICE guidelines (40 ppb) and is considered more useful because it is characterized by greater specificity, although less sensitivity (17); this is particularly important if considering that atopic patients may show an increase in FeNO during the pollen season, especially in polysensitized individuals where a dramatic increase was observed (26).

Importantly, FeNO testing is part of the diagnostic work-up in the GARD (Global Alliance Against Chronic Respiratory Diseases) recommendations for the management of severe asthma (27) and is included in the essential levels of assistance (LEA) in Italy, *i.e.*, the services and benefits that the National Health Service (SSN) is required to provide to all citizens.

The higher the FeNO value measured, the greater the probability of asthma (17). However, a negative test does not exclude asthma, especially if the patient has taken oral glucocorticoids or used ICS regularly or as needed (28). On the other hand, high FeNO levels may also be observed in non-asthmatic respiratory conditions, as eosinophilic bronchitis and allergic rhinitis (5, 29). In the proposed diagnostic work-up, FeNO measurement is suggested before bronchial challenge, as its execution is simpler, although its use is not widespread due to lack of the adequate equipment. The eosinophil count was not included as a diagnostic test, even if data are available in this regard, because of the variability of cut-off values between studies (3.4% and 360, 150, 500, 300 eosinophils/mmc) (25, 30-32); nevertheless, it is an important factor that may enhance the pre-test probability of confirming a diagnosis of PIA. The bronchial allergen challenge is not mentioned in the algorithm as, due to both safety and cost-efficiency concerns, its use is currently restricted to specialized centers with experienced staff, with protocols tailored to mild asthmatics for research purposes.

In conclusion, the probability of diagnosis of PIA phenotype can vary significantly in the pollination period, in which sensitized patients are symptomatic, as compared to asymptomatic periods outside the pollen season. Therefore, negative diagnostic tests should be contextualized with the presence of symptoms and the pollen calendar, to reduce the possibility of false negative diagnoses.

Risk stratification and control assessment in the pollen-induced asthma phenotype

Asthma control includes two domains: symptoms (impairment) and future risk (5, 33, 34). The assessment can be carried out with validated questionnaires, such as the ACT, which investigates a previous period of 4 weeks. In the PIA phenotype, the results on symptoms (impairment) can be highly discordant if carried out in a period of exposure to pollen compared to a period outside and far from the pollen season. Similarly, the interpretation of the "future risk" reflects the same peculiarity because, unlike other forms of asthma, in this phenotype the major trigger factor for exacerbations, *i.e.*, pollen exposure, is clearly identifiable and directly correlated, in a quantitative measure, to the risk of exacerbations (**figure 2**). Therefore, the information obtained from assessment tools should be contextualized to the period of the year investigated and the pollen calendar.

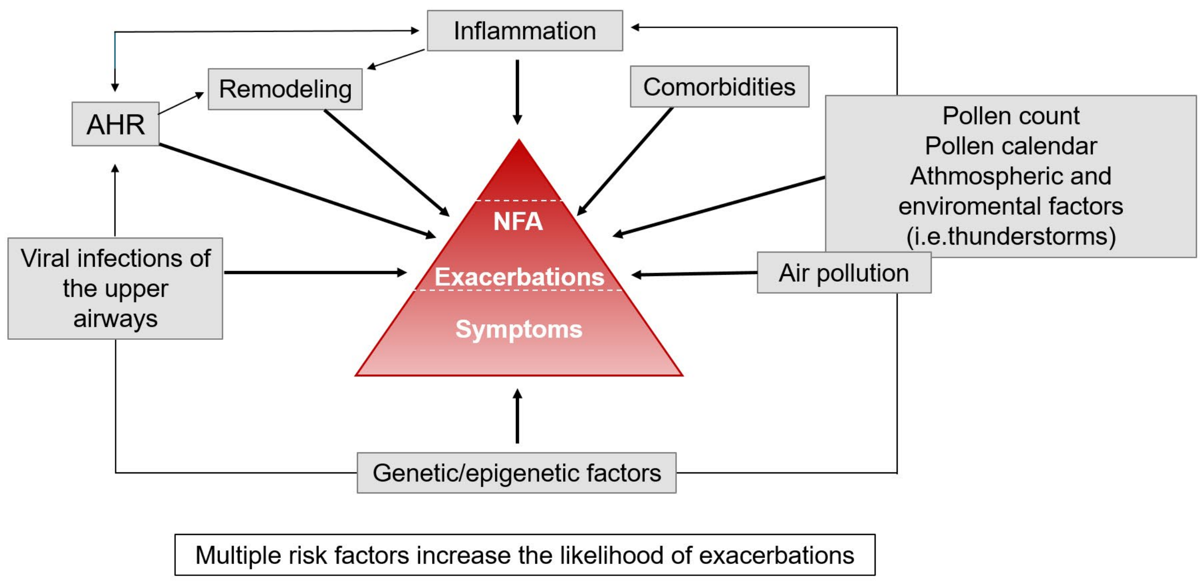
The predictability of the main future risk plays a central role in the clinical management of PIA. Even patients with mild asthma may experience episodes of severe exacerbations (5). Indeed, a significant proportion of subjects who have experienced episodes of "near-fatal asthma" or death from asthma were atopic and were classified as mild asthmatics, frequently not taking any controller ICS-based therapy (5, 35), suggesting that the impairment domain and the future risk domain are not closely related (36-38). These observations suggest that in PIA the risk stratification should be carried out in the pre-seasonal period, to identify the most suitable pharmacological strategy.

Figure 2 summarizes the factors associated with an increased risk of exacerbations in patients with PIA.

An accurate medical history can be sufficient to identify subjects who are more likely to develop symptoms and are at risk of exacerbations during periods of maximum exposure to pollen.

Notably, symptoms that are proxies of exacerbations and are possible markers of AHR, that affects the extent of the broncho-

Figure 2 *- Risk factors for exacerbations in pollen-induced asthma.*



NFA: near-fatal asthma; AHR: airway hyperresponsiveness

spasm response to inhaled allergens, should be carefully identified (22, 39). They include wheezing, chest tightness, shortness of breath, and nocturnal awakenings.

From a clinical perspective, the main risk factor is a history of exacerbations in the previous year, in particular during the pollen season. Both severe exacerbations, easier to detect and remember because they are characterized by the use of oral steroid therapy, and moderate exacerbations, mostly characterized by an increased frequency in the use of reliever drugs (34), should be assessed. Exacerbations are the result of the concomitance of multiple risk factors: exposure to pollen acts both as a predisposing factor, increasing T2 inflammation and AHR, and as a trigger for symptoms (40).

The onset of symptoms and, to a greater extent, an exacerbation, varies from subject to subject and in the same subject over time due to the co-presence or absence of different predisposing factors (genetic and epigenetic) and triggers, mostly pollen-related factors in PIA, in addition to the others (**figure 2**). This multifactorial contribution explains the high possible variability of seasonal symptoms (41-43).

In addition to previous exacerbations, for risk stratification it is useful to investigate the symptoms that occurred during the previous pollen season and their frequency. The most specific symptom is wheezing, an indicator of the presence of a significant obstruction (44, 45), although there is no clear correlation between obstruction and the onset of wheezing. Therefore, wheezing is a cardinal symptom to be assessed both in the previous pollen season and in the months preceding the control examination, reflecting a significant degree of bronchoconstriction.

The presence of wheezing, coughing and chest tightness are associated with AHR especially if they appear occasionally after episodes of hyperventilation, as during running in children and young adults, or when the patient sings or speaks loudly for a long time (46-48).

A further element to assess is the persistence of respiratory symptoms (as cough, chest tightness) after viral infection of the upper airways, which the patient often does not pay attention to, believing it to be a normal evolution of the infection (41).

Correct perception of the obstruction by the patient is an important factor in evaluating the reliability of the reported symptoms. In clinical practice, hypoperception can be identified in the presence of a discrepancy between the level of obstruction verified by spirometry and the symptoms reported, or more generally by an overestimation of the patient's control of symptoms compared to the evaluation of control obtained through questionnaires such as ACT, all factors that may increase the risk of exacerbations (49, 50).

The presence of comorbidities, in particular allergic rhinitis, gastro-esophageal reflux and obesity, also influence the risk of exacerbations (41).

Risk stratification can be further improved by using biomarkers related to bronchial inflammation: the greater the degree of inflammation in the pre-seasonal period, the greater the probability that the further release of T2 cytokines induced by allergic reactions can trigger seasonal symptoms.

High levels of FeNO reflect the presence of T2 inflammation and are indicators of positive response to ICS therapy. In previous versions of ERS/ATS guidelines, FeNO levels are considered low below 25 ppb, intermediate between 25-50 ppb and high > 50 ppb (28). Therefore, in patients with PIA, the finding of levels above 25 ppb in a period of non-exposure to pollen may be considered an indicator of future risk, and values above 40-50 ppb high risk; asymptomatic sensitized subjects in the period of non-exposure to pollen generally do not have significantly increased FeNO levels (26).

Different FeNO thresholds have been used, in mild allergic asthmatic subjects with FeNO values lower than the cut-off value and with positive clinical outcomes, to predict the possibility of reducing/suspending ICS (51, 52).

Regarding circulating eosinophils, large studies (Copenhagen General Population Study) including to a greater extent patients with mild asthma, indicate that high levels (400 eosinophils/mm^3) predict an increased risk of serious exacerbations and poor asthma control (53, 54). In addition, the *post-hoc* analysis of the Atlantis study showed that 16% and 26% of patients with mild asthma, respectively in the GINA 1-2 steps, have a post-bronchodilator FEV1/FVC < LLN and this functional impairment is related to eosinophilic inflammation and an increased risk of exacerbations (55).

The concomitant presence of high levels of FeNO and circulating eosinophils is also useful to identify subjects with greater risk of exacerbations. However, it should be noted that also smokers may show higher levels of circulating eosinophils and low levels of FeNO (56, 57).

The presence of an AHR together with allergic sensitization is known to be a prerequisite for the development of an early allergic response in terms of airway obstruction (58-60). High levels of AHR, especially if detected prior to the pollination season, also may constitute an important risk factor for the development of symptoms and exacerbations during maximum exposure to pollen (39, 61-68). Importantly, the finding of a concomitant fall in FEV1 and FVC during the bronchial challenge with methacholine allows to identify patients, even those suffering from mild asthma, who are at risk of episodes of near-fatal asthma, as there is a concomitant obstruction of the proximal and distal airways which can lead to respiratory arrest (69, 70).

Adherence to asthma medication during the pollen season

Although in clinical studies asthma can be well controlled in most patients with an appropriate therapeutic strategy (71), in clinical practice non-adherence with prescribed medications is very common and represents a significant barrier to optimal disease management.

To date, scientific literature does not report data on the adherence to medication in patients specifically affected by PIA. The available evidence comes from studies conducted on patients with allergic (sensitive to pollen or other allergens) or non-allergic asthma. In any case, the problem of therapeutic adherence appears to be independent of the trigger factors. Therefore, the findings emerging from these studies may be transferable to PIA.

Approximately 50% of adults and children on long-term therapy for asthma fail to take medication at least part of the time, resulting in poor quality of life, reduced work performance, and increased risk of exacerbation, associated with increased direct and indirect costs of disease management (5, 72, 73). Adherence may also decrease over time: a real-world study showed that adherence significantly declined with subsequent prescriptions (74). Furthermore, undetected suboptimal adherence, including the correct use of the inhalers, may be interpreted as poor therapeutic response, perpetuating a cycle of uncontrolled asthma symptoms, review and therapy escalation (75-77).

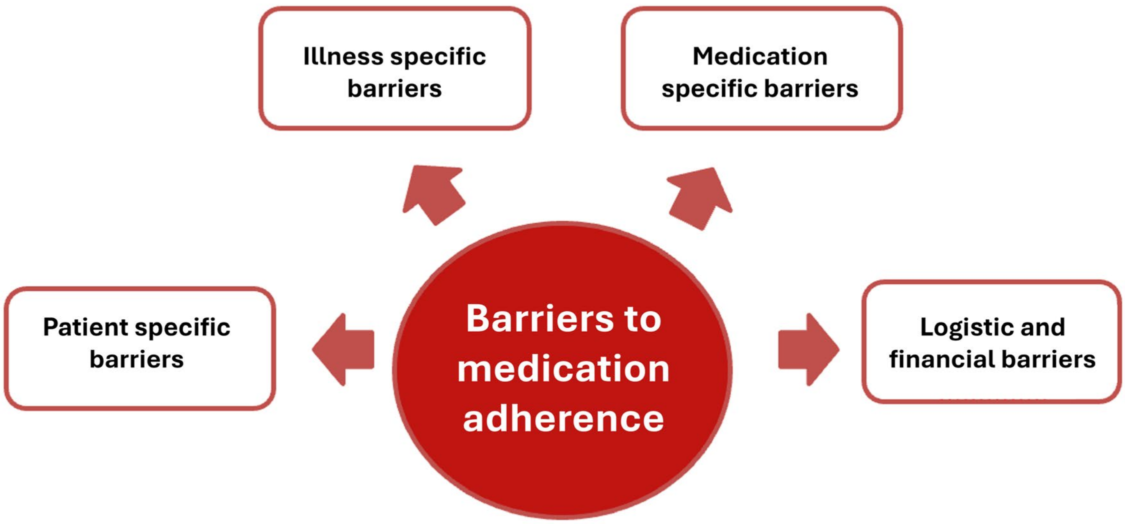
Several factors may influence therapeutic adherence and persistence, like personal and individual factors, psychological issues, health beliefs and behaviors, the clinician-patient relationship, factors linked to the disease (progression, stability, exacerbations), to the treatment (complexity of current medications, difficult-to-use inhaler, frequency of dosing, side-effects), or to costs and access (**figure 3**) (5, 78, 79).

The simplification of the therapeutic regimen, with prescription of once daily medications and easy-to-use inhalers, are important factors for achieving good compliance (5, 80).

On the other hand, several studies suggest that one of the determinants of poor adherence is the perception that the medication should be used in response to symptoms more than on a regular basis (81-83). Not surprisingly, treatment discontinuation is significantly higher in those who seek medical assistance for symptom worsening. The findings reflect an incongruence between the medical perspective, emphatizing proactive control through prevention of symptoms and exacerbations, and the patient's perspective, where to some extent symptoms are regarded as part of having asthma, rather than a sign that their asthma is poorly controlled (84).

In the case of allergen immunotherapy (AIT), a period of repeated administration for at least 3 years is required for achieving sustained symptom relief and potentially altering the disease course. This long-term commitment can be challenging for patients to maintain. Indeed, despite long term benefits, real life studies on

Figure 3 *- Key barriers to medication in chronic disease.*



Adapted from Kvarnström *et al.* 2021 (79).

patients with allergic rhinitis and asthma showed that at 3 years the overall adherence to AIT was below 40% (85, 86). Adherence was higher in the first year of treatment, in children and, in some studies, with the subcutaneous formulation (SCIT) *versus* the sublingual formulation (SLIT) (85, 86). Reasons for treatment discontinuation are due to factors like long duration of treatment, need for regular injections or daily sublingual administration, perception of poor efficacy, costs, and potential side effects (85, 86). In conclusion, evidence on the adherence to medication regimens in patients specifically affected by PIA is poor. On the other hand, therapeutic adherence in asthma remains a recurrent problem, regardless of the trigger factor.

Risk of (severe) exacerbations: the unpredictability of exposure

Pollen exposure is one of the factors associated with worsening of the symptoms of allergic rhinitis and asthma (87). The impact of pollen on respiratory health can be particularly significant in children, given that more than half of pediatric asthma cases are thought to have an allergic component (40, 88).

In the study by De Roos *et al.* (89) on subjects aged < 18 years followed over a 5-year period, an increased odd of asthma exacerbation was found in association with the exposure to tree pollen. Even low pollen levels (≤ 5 grains/m^3) were associated with small risk, with an exposure-response pattern of increasing odds with higher pollen level. A 64% increased risk was observed at pollen levels > 1,000 grains/m^3; for grasses, asthma exacerbations were associated with exposure to 52 grains/m^3 of pollen, while no correlation was shown with exposure to ragweed pollen and other pollen.

An Australian study by Shrestha *et al.* (90) assessed the role of ambient levels of different pollens on hospital admissions for asthma over a 5-year period in 2,098 children and adolescents. The results showed a significant correlation between Plantago and Parietaria pollen peaks and the rate of hospitalization for bronchial asthma, especially in younger children of 2-5 years of age; specifically, an increase in pollen concentration of 50 grains/m^3 was strongly associated with the risk of hospitalization. Similarly to other studies, a trend toward a greater pollen effect was observed in boys. The correlation was higher in colder seasons, but this finding could also be related to viral infections, so it is unclear whether pollen stimulation was the primary trigger.

The association between outdoor pollen and childhood asthma hospitalizations was examined in a systematic review (91). Although there was a substantial heterogeneity among studies related to pollen species, geographical areas, method of analysis used to estimate the effect size and differences in lagged day effects considered for the analysis, the results showed that globally grass and birch pollen were important triggers of childhood asthma hospitalization: an increase in 10 grass pollen grains/m^3 was associated with a 3% increase in admissions for asthma and an extreme pollen day (> 100g/m^3) could lead to a 30% increase in hospitalizations for asthma.

Interestingly, a study on a large cohort of 47,456 children admitted to hospital for asthma showed that grass pollen exposure was associated with higher readmission rates for asthma, supporting

the importance of target interventions for asthmatic children prior the pollen season (92).
In the study by Lappe *et al.* (93) covering a 26-year period of observation, a strong association was found between 9 of the 13 pollen varieties analyzed (grasses, nettle, pigweed, birch, maple, pine, oak, willow, sycamore, mulberry) and Emergency Departement (ED) visits for asthma and wheeze, with a 1-8% increase in ED admissions per standard deviation increases in pollen, which is consistent with the results from other studies (94). In general, the strongest association was observed in younger people and in Afro-Americans subjects, although the data varied by pollen taxa. Birch pollen was shown to be associated to asthma exacerbations especially in Northern European countries and North America. A Swedish study found an increase in respiratory symptoms and use of respiratory drugs alongside a reduction in lung function parameters during the pollen season (95). Moreover, pollen exposure increased the susceptibility to adverse respiratory effects induced by pollutants (particulate matters and O_3).
The epidemiological prospective study by Dominiguez-Ortega (96) compared clinical, functional and pathophysiological outcomes during and outside the pollen season in 101 adults diagnosed with allergic asthma and rhinitis who manifested exclusively seasonal symptoms caused by grasses and/or olive tree. The results show that most patients experienced symptoms, lung function abnormalities and airway-inflammation (as reflected by measurement of FeNO) exclusively during the pollen season, although a few continue to experience abnormalities outside the exposure period.
The occurrence of thunderstorms during pollen season of some taxa may lead to the so called “thunderstorm asthma”, an epidemic of allergic asthma outbreaks, sometimes also severe asthma attacks, as reported in many areas of the world (97). The Melbourne thunderstorm asthma epidemic during the peak grass pollen season in November 2016 was unprecedented in scale and impact, with a large number of people having breathing difficulties and about 9900 patients’ presentations at hospital emergency departments (98, 99). A systematic analysis of hospital’s patients in Melbourne aged ≥16 years with thunderstorm asthma was conducted by Lee *et al.* (98), to identify key risk factors. Of 85 adult patients assessed, the majority (60%) had no prior diagnosis of asthma. However, allergic rhinitis during the grass pollen season was almost universal (99%), as were ryegrass pollen sensitization (100%) and exposure to the outdoor environment during the thunderstorm (94%). Airborne pollen levels on the thunderstorm day were extreme (102 grains/m^3) (98). The results suggest that ryegrass pollen sensitization and clinical allergic rhinitis define the adult population at risk for thunderstorm asthma, with acute allergen exposure as a trigger factor. The size of ryegrass pollen grains is > 35 μm in diameter, but stormy moisture may cause their rupture into respirable 3 μm granules that can easily penetrate deeply into the airways and elicit respiratory symptoms in predisposed subjects.
Based on this evidence, thunderstorm asthma can be considered a model of PIA and a risk factor of severe exacerbations in patients with mild asthma, often undiagnosed, allergic asthma.

The management of pollen-induced asthma: a model of regular treatment?

The aim of asthma management should be to achieve the best possible long-term outcomes for the individual patient. This may include significant reduction (possibly the complete absence) of asthma daytime and nocturnal symptoms, to improve lung function, to prevent/minimize the risk of acute deterioration of asthma symptoms (exacerbations) and asthma-related death, provide optimal pharmacotherapy with a simple dosage schedule and minimal or no adverse effects and to allow the patients to have a normal or almost normal life. According to that, asthma may be considered under control when all these outcomes are achieved (5, 100-104).
Poor symptom control of asthma is associated with an increased risk of exacerbations, but even people with good symptom control or seemingly mild asthma can still be at risk of severe exacerbations (105), and even death (106). Thus, most guidelines recommend that asthma control should be assessed in two domains: 1) current symptom control and 2) risk factors for future poor asthma outcomes, particularly exacerbations (*e.g.*, smoke, history of exacerbations, blood eosinophilia or high FeNO, environmental exposure) (5, 100-104).
The definition of asthma control mostly refers to the stability of clinical and functional parameters. However, some authors suggest that the inflammatory profile of an asthmatic patient should also be considered in the evaluation of asthma control (107). In this regard, within populations of patients with allergic rhinitis or intermittent asthma, some subjects show evidence of ongoing bronchial inflammation, *i.e.*, low pH and high IL-5 concentrations in the exhaled breath condensate, as well as increased FeNO levels (107, 108).
The question whether subclinical airway inflammation may determine the risk of relapse later in future was addressed in a large population-cohort study (109). The results demonstrated that a number of inflammatory biomarkers was independently associated with future respiratory outcomes or accelerated lung function decline. In this respect, GINA document points out that increased levels of type 2 inflammatory markers are risk factors for poor asthma outcomes (5).
It should be also underlined that each bronchoconstrictor event determines epithelial and bronchial muscle stress (mechanotransduction), which translates into the release of cytokines and growth factors that accelerate bronchial remodeling and inflammation, generating positive feedback mechanisms that tend to

perpetuate the persistence of asthma (110-114). These findings have potential implications for asthma management, as the prevention of bronchoconstriction itself could be an important target, contributing to the reduction of inflammation.
As a consequence, ideal treatment strategies should be also aimed at controlling underlying airway inflammation and possibly prevent or slow down remodeling processes.
Inhaled corticosteroids (ICS), alone or in single inhaler combination with long acting beta2 agonists (LABA), are the mainstay of asthma treatment and are recommended in several national guidelines as regular preventive therapy approach, in which the dose of ICS is appropriate to the severity of disease and can be increased as necessary, and decreased, when possible, to achieve and maintain disease control (100-104). The frequency of rescue medication use, such as the short acting beta2 agonists (SABA) to relieve symptoms, is considered a reliable measure of asthma control.
In mild-moderate asthma, the guidelines also consider the use of a single combination inhaler of ICS/LABA for maintenance and reliever therapy (MART), which might suit some individuals (5). It relies on the rapid onset of reliever effect with formoterol and by including a low dose of inhaled corticosteroid it ensures that, as the need for a reliever increases, the dose of preventer medication is also increased.
The analysis of MART clinical trials demonstrated that this strategy was at least as effective as a regular treatment with other ICS/LABA combinations plus SABA as needed in the prevention of severe exacerbations, but it is associated with a significant level of symptoms (54% of the days) and frequent use of rescue medication, that may be considered as a sign of an incomplete asthma control, particularly when these events are frequently reported (115-119). Notably, Pavord *et al.* (120) showed that sputum eosinophils and endobronchial biopsy eosinophils were significantly lower following a regular treatment with ICS/LABA plus SABA compared to MART strategy, where a trend towards increased cellularity was observed.
Interestingly, three surveys have been conducted in 16 countries all over the world to understand current treatment approaches for patients with asthma and how these align with the latest GINA recommendations in real-world clinical practice. Altogether 2,482 physicians (mainly pulmonologists and general practitioners) and 4,266 asthmatic patients have been enrolled (121-123). The results show important rates of poor asthma control and SABA use across all participating countries. Patients appear to overestimate their level of asthma control, that is not aligned with their reporting of symptoms/limitations. Physicians generally rated symptom control over exacerbation reduction as their main treatment goal for patients with mild to moderate asthma. This was consistent with prioritization of symptoms over exacerbations when prescribing daily maintenance medication. The consolidated proactive treatment with ICS/LABA and as-needed SABA remains the preferred initial approach. Furthermore, the co-prescription of MART therapy and SABA (frequently requested by the patients themselves) suggests confusion between reliever strategies in real world or alternatively is suggestive of patients who may remain uncontrolled on MART therapy and feel the need for a reliever to manage their asthma symptoms (122).
Another aspect to be considered is the hypoperception of airway obstruction by the patients that was reported in approximately 26% of asthmatics; these patients are poor judges of their clinical conditions, and this under-estimation may lead to poor adherence to maintenance therapy, inadequate treatment of airway inflammation and airway hyperresponsiveness and increased risk for exacerbations and episodes of near-fatal asthma.
However, the model of pharmacological treatment proposed in the guidelines, largely based on a similar type of therapeutic response for all patients, does not consider, in mild-moderate asthma, the possible different phenotypes that may require a personalized approach. In this respect, the PIA phenotype is pathognomonic, as the assessment of the impairment domain (symptoms), on which the control assessment is largely based, varies considerably depending on the exposure period to pollen, given that the questionnaires (such as ACT) often investigate the symptoms relating to the previous few days or weeks.
Furthermore, unlike other clinical phenotypes, in PIA the main future risk factor, the seasonal exposure to pollen, is known and partly predictable. This consideration is, however, still insufficient for a rational therapeutic approach, which cannot necessarily be the same in all periods of the year and in all subjects.
For this reason, we have proposed the need to carry out a seasonal risk stratification, based on the risk factors of exacerbation previously described and shown in **figure 2**, using the considerations summarized in **table I**.
Consequentially, the proposed therapeutic algorithm that considers the risk stratification model is schematized in **figure 4**.
In subjects at low risk, ICS/formoterol as needed or low dose ICS whenever SABA is taken can be considered. In the event that the use of the rescue medication is > 2 days/week or in case of symptoms ≥ 2 days/week, it is recommended to switch to a fixed daily therapy.
In subjects stratified as high risk, we propose a maintenance daily therapy with ICS/LABA and SABA as needed, or daily maintenance ICS and as needed SABA or MART with ICS/formoterol from the beginning of the exposure period, determined on the basis of the pollen calendar. The strength of ICS (medium or high) is determined by the healthcare professional based on risk stratification; generally, in patients with PIA a medium strength is sufficient. In any case, the rapid variability of pollen exposure conditions can make it difficult to obtain a maximal bronchoprotective effect using a symptom-driven approach, as this achievement requires therapeutic continuity. In addition, the persistence of risk factors for the loss of asthma control, including comorbidities and increased biomarkers of airway inflammation, even in

***Table I** - Seasonal risk stratification.*

	Indicators	High risk	Low risk
Symptoms during pollen exposure	Severe exacerbations in the previous 12 months	≥ 1	None
	Frequency of respiratory symptoms	≥ 1 time/week	None
	Use of reliever	Regularly > 1 time/week	No, a few times
Symptoms before pollen season	Persistent (> 1 week) respiratory symptoms* after airway viral infection	Yes	No
	Respiratory symptoms* after hyperventilation (running, singing…)	Yes	No
	Respiratory symptoms* in the current and previous months	Yes	No
Biomarkers assessed before pollen season	FeNO	≥ 40 ppb	< 25 ppb
	Eosinophils	≥ 400 /mmc	< 150 /mmc
Lung function before pollen season	Spirometry: airway obstruction	FEV1/FVC < LLN or < 75%	FEV1/FVC ≥ LLN or ≥ 75%
	Spirometry: FEV1	< 80% predicted or > 10% fall *versus* previous control	Normal or ≥ 80% predicted unchanged from personal best
	Spirometry: bronchial responsiveness test	≥ 12% and 200 ml	< 12% and 200 ml
	Direct bronchial challenge (PC20)	High AHR: PC20 < 1 mg/ml Moderate AHR: PC20 ≥ 1 ≤ 4 mg/ml	Mild AHR > 4 ≤ 8 mg/ml AHR borderline > 8/mg/ml
	Indirect bronchial challenge (PD15)	Positive to mannitol test: PD15 ≤ 635 mg mannitol	Negative to mannitol test: PD15 > 635 mg mannitol
Other clinical features to consider	^Moderate-severe allergic rhinitis, rhinosinusitis, gastroesophageal reflux, obesity Impaired perception of bronchoconstriction (hypo-perceptors); perception reduced also in patients with high AHR		

*Respiratory symptoms: cough, shortness of breath, wheezing, chest tightness; ^the risk increases if multiple comorbidities are present; AHR: airway hyperresponsiveness.

a patient with apparently minor daily symptoms, should be also considered for treatment optimization, to prevent negative outcomes. Therapy will be withheld or reduced based on the progression of symptoms and the resolution of triggering factors, supported by the pollen data.

In patients with PIA receiving seasonal therapy it is advisable to use a principle of maximum precaution, in particular in those considered at high risk, as they may experience severe exacerbations or even episodes of near-fatal asthma due to the rapid changes in the allergenic load to which they are exposed, in the presence of a high degree of AHR not previously highlighted and undertreated with ICS (35-37). In this respect, modeling studies based on published experimental and clinical data showed that a different degree of asthma control and bronchoprotection (*i.e.*, suppression of the AHR) as well as systemic activity can be achieved depending on the adherence to the therapeutic regimen and the type of ICS used (124).

None of the above-mentioned pharmacological therapies address the pathogenetic mechanism of allergic asthma. Conversely, AIT is the only therapeutic intervention able to induce both immune modifying effects and long-term efficacy.

Different efficacy results have been reported in relation to heterogeneity in terms of products used, routes of administration (subcutaneous – SCIT and sublingual – SLIT), study populations, and study designs compared to those commonly employed in pharmacological clinical trials of asthma (125, 126).

The efficacy of AIT in seasonal allergic asthma caused by grass pollen allergy and tree pollen allergy (the most frequently studied pollens considering their epidemiological load) has been proven in clinical trials and real-word studies, especially with SCIT (127-129).

The large retrospective cohort study REACT analyzed German health insurance data from 2007 to 2017: the analysis showed that AIT prescription in patients with allergic asthma (compared with a control group without AIT prescription) led to a lasting improvement in asthma control, lower medication consumption, and a decrease in the exacerbation rate (127). In addition, these effects even increased over time after the end of AIT and there was also an advantage for patients with asthma with regard to the occurrence of pneumonia and hospitalizations.

A population-based Danish study compared patients with asthma who received an AIT prescription with patients who did not receive an AIT prescription: in the 3 years following completion of the AIT prescription, there was a sustained reduction in the exacerbation rate (on average by 74% in patients with seasonal allergies and on average by 57% in patients with house dust mite allergies) compared with patients without an AIT prescription (128).

The results of a real-world study involving a large sample of patients showed that sublingual AIT was associated with a significant reduction in the risk of new asthma events for up to eight years and also in the risk of asthma onset or worsening, for all ages and allergens evaluated (129). The results support the long-term effectiveness of sublingual AIT treatment of patients with allergic rhinitis with and without pre-existing asthma, as a relevant causal option for patients with respiratory allergies.

AIT is currently recommended for allergic asthma, if it is well documented that allergens elicit asthma symptoms and if asthma is controlled (130). Thus, AIT is considered as an additional therapy for allergic asthma, and carried out after the initiation of adequate drug therapy for asthma. Ideally, inhaled therapy can be reduced during AIT or even stopped completely once AIT has been completed.

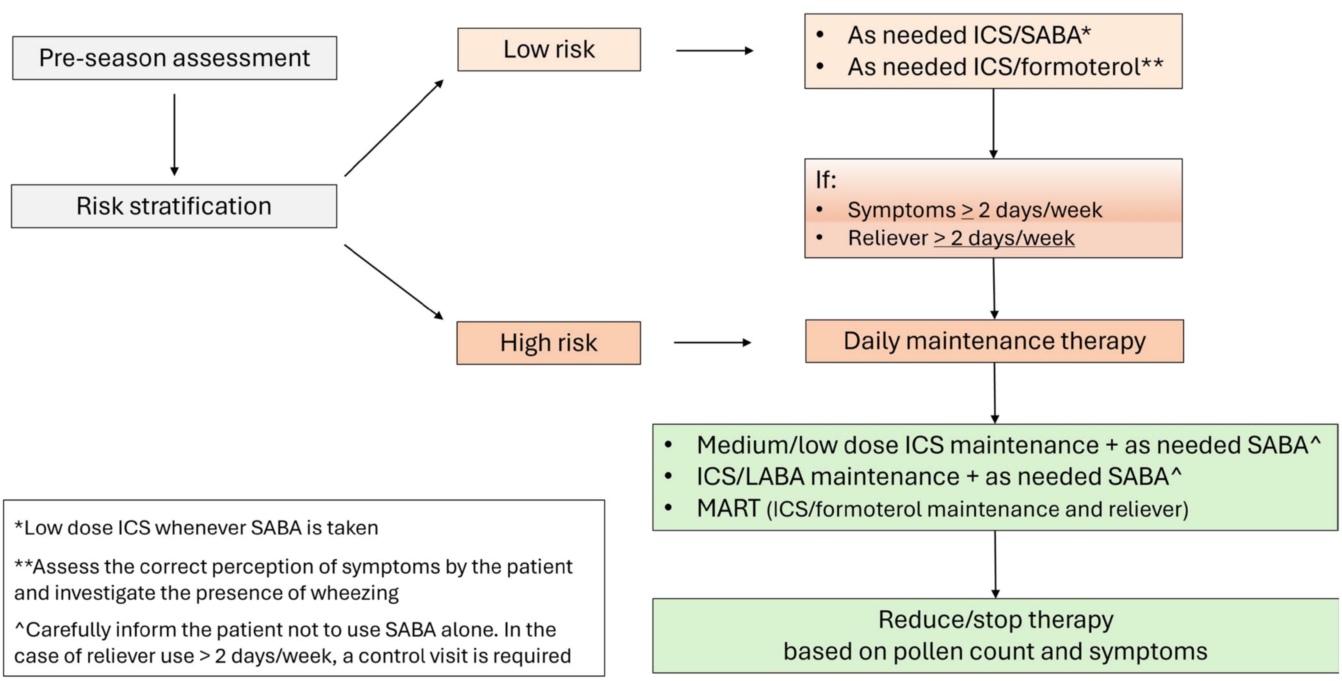
However, in case of patients with symptoms limited to the pollen season, AIT should be associated to a proper treatment according to the PIA therapeutic algorithm (**figure 4**).

Conclusions

Evidence supports the hypothesis of PIA as a specific asthma phenotype, characterized by substantial asymptomatic periods in which patients are not exposed to triggers, with allergic rhinitis being one of the most common comorbidities.

Although the pollen season represents the key factor affecting the risk of asthma outbreaks, pollen count, aerobiological data, the presence of polysensitivity that can overlap, and the meteorological conditions can also influence the clinical picture of the patients in different directions (38). In this context, a careful assessment of the clinical manifestations in the previous year and in the period before the pollen season, as well as the measurement of objective markers (FeNO, AHR, FEV1, circulating eosinophils), make it possible to stratify the risk of symptoms and exacerbations, allowing the therapeutic approach to be tailored in a rational manner during the seasonal exposure period.

Figure 4 *- Therapeutic algorithm for pollen-induced asthma.*



Effective disease control can be achieved through the use of therapeutic regimens containing ICS. Depending on patients' characteristics and risk factors, healthcare professionals and patients can share the decision on the best therapeutic strategy (131), considering effective bronchoprotection and the simplicity of regular once-daily administration of ICS/LABA, that favors the therapeutic adherence (132), and the flexibility of the MART strategy, which however may require more careful education and collaboration from the patient (133). In patients who, in previous years, have shown a loss of asthma control only in the season when they are exposed to sensitizing allergens, a seasonal therapy (*i.e.*, therapy prescribed during periods of seasonal exposure) may be considered (133). In any case, the poor predictability of exposure to pollen, with its variations in concentration and allergenicity, highlights the importance of a preventive approach to reduce the risk of asthma outbreaks. Thus, starting daily therapy with low-dose ICS/LABA before the period of maximum allergic exposure could be advisable to increase the level of bronchoprotection (133).

Allergen-specific immunotherapy is the only curative treatment that can be used in association with standard pharmacological therapy in PIA, that may provide benefit, especially in subjects with comorbidities, such as allergic rhinitis, and may reduce drug burden (134).

Educating patients on proper symptom perception and adherence to treatment is also crucial for optimal disease control.

Fundings

GlaxoSmithKline S.p.A. provided financial and human resources to support the implementation of the project "The patient with pollen-induced asthma: from the unpredictability of risk to a possible management model". The company has been granted an exclusive license by AAIITO (Italian Association of Territorial and Hospital Allergologists and Immunologists) to access and use the information, results, and materials derived from the project.

Contributions

All authors equally contributed to the manuscript draft and critical revision for important intellectual content, to data collection, analysis and interpretation.

Conflict of interests

LC reports personal fees from Chiesi Farmaceutici (consulting), Thermofisher (consulting, talks), GlaxoSmithKline (consulting, talks), Astra Zeneca (consulting, talks), Menarini (talks, consulting), Novartis (consulting, talks), and Sanofi (consulting, talks). AM reports personal fee from Sanofi (talks) and GSK (consulting). KJ reports personal fee from Sanofi (talks) and GSK (consulting). AMM reports personal fees from GlaxoSmithKline (consulting). MM reports personal fees from Chiesi Farmaceutici (consulting), GlaxoSmithKline (consulting, talks), and AstraZeneca (consulting). AV reports personal fees from Chiesi Farmaceutici (talks), GlaxoSmithKline (talks), AstraZeneca (talks), and Menarini (talks). MBB reports personal fees from ALK (consulting), AstraZeneca (talks), BluePrint (advisory board, talk), Gentili (talk), GSK (talks), Menarini (talks), and Sanofi (advisory board, talks). FP, GV, and BY report no conflict of interest.

References

1. Cecchi C, Martini, Jaubashi K, Maria Marra AM, Papia F, et al. Pollen-induced asthma: a specific pheno-endotype of disease? Eur Ann Allergy Clin Immunol. 2025;57(5):xxx-xxx. doi: 10.23822/EurAnnACI.1764-1489.403.
2. Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019;56(2):219-33. doi: 10.1007/s12016-018-8712-1.
3. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: Moving toward precision medicine. J Allergy Clin Immunol. 2019;144(1):1-12. doi: 10.1016/j.jaci.2019.05.031.
4. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010;182(5):598-604. doi: 10.1164/rccm.200912-1843CC.
5. Global Initiative for Asthma Management and Prevention (GINA) – update 2024. Available at: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf.
6. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181(4):315-23. doi: 10.1164/rccm.200906-0896OC.
7. Lefaudeux D, De Meulder B, Loza MJ, Peffer N, Rowe A, Baribaud F, et al. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. J Allergy Clin Immunol. 2017;139(6):1797-807. doi: 10.1016/j.jaci.2016.08.048.
8. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218-24. doi: 10.1164/rccm.200711-1754OC.
9. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. Semin Immunol. 2019;46:101333. doi: 10.1016/j.smim.2019.101333.
10. Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004;113(1):86-93. doi: 10.1016/j.jaci.2003.10.010.
11. Manzanares B, González R, Serrano P, Navas A, Alonso C, Fernandez L, et al. Back to basics: likelihood ratios for olive and grass pollen specific IgE in seasonal allergic rhinitis. Front Allergy. 2023;4:1241650. doi: 10.3389/falgy.2023.1241650.
12. Xie ZJ, Guan K, Yin J. Advances in the clinical and mechanism research of pollen induced seasonal allergic asthma. Am J Clin Exp Immunol. 2019;8(1):1-8.
13. Callery EL, Keymer C, Barnes NA, Rowbottom AW. Component-resolved diagnostics in the clinical and laboratory investigation of allergy. Ann Clin Biochem. 2020;57(1):26-35. doi: 10.1177/0004563219877434.

14. Dramburg S, Hilger C, Santos AF, de Las Vecillas L, Aalberse RC, Acevedo N, et al. EAACI Molecular Allergology User's Guide 2.0. Pediatr Allergy Immunol. 2023;34 Suppl 28:e13854. doi: 10.1111/pai.13854.
15. Asthma: diagnosis, monitoring and chronic asthma management (BTS, NICE, SIGN). London: National Institute for Health and Care Excellence (NICE); 2024.
16. Louis R, Satia I, Ojanguren I, Schleich F, Bonini M, Tonia T, et al. European Respiratory Society guidelines for the diagnosis of asthma in adults. Eur Respir J. 2022;60(3):2101585. doi: 10.1183/13993003.01585-2021.
17. National Institute for Health and Care Excellence (NICE). NICE guideline NG80. Asthma: diagnosis, monitoring and chronic asthma management. 29 November 2017. Available at: https://www.nice.org.uk/guidance/ng80.
18. Vaghi A, Bilò MB, Bini F, Cecchi L, Micheletto C, Musarra A. The added value of targeting airway hyperresponsiveness by blocking TSLP in the management of severe asthma. Eur Ann Allergy Clin Immunol. 2024. doi: 10.23822/EurAnnACI.1764-1489.376. Epub ahead of print.
19. Cockcroft DW. Direct challenge tests: Airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest. 2010;138(2 Suppl):18S-24S. doi: 10.1378/chest.10-0088.
20. Chapman DG, Irvin CG. Mechanisms of airway hyper-responsiveness in asthma: the past, present and yet to come. Clin Exp Allergy. 2015;45(4):706-19. doi: 10.1111/cea.12506.
21. Prieto L, Bertó JM, Lopez M, Peris A. Modifications of PC20 and maximal degree of airway narrowing to methacholine after pollen season in pollen sensitive asthmatic patients. Clin Exp Allergy. 1993;23(3):172-8. doi: 10.1111/j.1365-2222.1993.tb00878.x.
22. Suh DI, Koh YY. Relationship between atopy and bronchial hyperresponsiveness. Allergy Asthma Immunol Res. 2013;5(4):181-8. doi: 10.4168/aair.2013.5.4.181.
23. Boulet LP, Turcotte H, Plante S, Chakir J. Airway function, inflammation and regulatory T cell function in subjects in asthma remission. Can Respir J. 2012;19:19-25. doi: 10.1155/2012/347989.
24. Cano-Garcinuño A, Carvajal-Urueña I, Díaz-Vázquez CA, Domínguez-Aurrecoechea B, García-Merino A, de Rodas PM, Mora-Gandarillas I. Clinical correlates and determinants of airway inflammation in pediatric asthma. J Investig Allergol Clin Immunol. 2010;20(4):303-10.
25. Louis G, Schleich F, Guillaume M, Kirkove D, Nekoee Zahrei H, Donneau AF, et al. Development and validation of a predictive model combining patient-reported outcome measures, spirometry and exhaled nitric oxide fraction for asthma diagnosis. ERJ Open Res. 2023;9(1):00451-2022. doi: 10.1183/23120541.00451-2022.
26. Olivieri M, Marchetti P, Murgia N, Nicolis M, Torroni L, Spiteri G, et al. Natural pollen exposure increases in a dose-dependent way Fraction of exhaled Nitric Oxide (FeNO) levels in patients sensitized to one or more pollen species. Clin Transl Allergy. 2022;12(2):e12096. doi: 10.1002/clt2.12096.
27. Elementi di indirizzo per la prevenzione e la gestione integrata dell'asma grave. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_3496_allegato.pdf.
28. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602-15. doi: 10.1164/rccm.9120-11ST.
29. Haccuria A, Michils A, Michiels S, Van Muylem A. Exhaled nitric oxide: a biomarker integrating both lung function and airway inflammation and airway inflammation changes. J Allergy Clin Immunol. 2014;134(3):554-9. doi: 10.1016/j.jaci.2013.12.1070.
30. Bao W, Zhang X, Yin J, Han L, Huang Z, Bao L, et al. Small-Airway Function Variables in Spirometry, Fractional Exhaled Nitric Oxide, and Circulating Eosinophils Predicted Airway Hyperresponsiveness in Patients with Mild Asthma. J Asthma Allergy. 2021;14:415-26. doi: 10.2147/JAA.S295345.
31. Koca Kalkan I, Koycu Buhari G, Ates H, Başa Akdoğan B, Özdedeoğlu Ö, Aksu K, et al. Can fractional exhaled Nitric Oxide with blood eosinophil count have a place in the diagnostic algorithm for Asthma? Asthma Allergy Immunol. 2021;19(2):100-9. doi: 10.21911/aai.643.
32. Livnat G, Yoseph RB, Nir V, Hakim F, Yigla M, Bentur L. Evaluation of high-sensitivity serum CRP levels compared to markers of airway inflammation and allergy as predictors of methacholine bronchial hyper-responsiveness in children. Lung. 2015;193(1):39-45. doi: 10.1007/s00408-014-9658-6.
33. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines.
34. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59-99. doi: 10.1164/rccm.200801-060ST.
35. Sekiya K, Nakatani E, Fukutomi Y, Kaneda H, Iikura M, Yoshida M, et al. Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis. Clin Exp Allergy. 2016;46(8):1043-55. doi: 10.1111/cea.12738.
36. Vianello A, Caminati M, Crivellaro M, El Mazloum R, Snenghi R, Schiappoli M, et al. Fatal asthma; is it still an epidemic? World Allergy Organ J. 2016;9(1):42. doi: 10.1186/s40413-016-0129-9.
37. D'Amato G, Vitale C, Lanza M, Sanduzzi A, Molino A, Mormile M, et al. Near fatal asthma: treatment and prevention. Eur Ann Allergy Clin Immunol. 2016;48(4):116-22.
38. Silver JD, Sutherland MF, Johnston FH, Lampugnani ER, McCarthy MA, Jacobs SJ, et al. Seasonal asthma in Melbourne, Australia, and some observations on the occurrence of thunderstorm asthma and its predictability. PLoS One. 2018;13(4):e0194929. doi: 10.1371/journal.pone.0194929.
39. Cockcroft DW, Murdock KY, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. Am Rev Respir Dis. 1987;135(1):264-7. doi: 10.1164/arrd.1987.135.1.264.
40. Schatz M, Rosenwasser L. The allergic asthma phenotype. J Allergy Clin Immunol Pract. 2014;2(6):645-8. doi: 10.1016/j.jaip.2014.09.004.
41. Wang L, Zhou L, Zheng P, Mao Z, Liu H. Mild asthma is not mild: risk factors and predictive biomarkers for severe acute exacerbations and progression in mild asthma. Expert Rev Respir Med. 2023;17(12):1261-71. doi: 10.1080/17476348.2024.2314535.
42. Ban GY, Kim SC, Lee HY, Ye YM, Shin YS, Park HS,Risk factors predicting severe asthma exacerbations in adult asthmatics: a real-world

clinical evidence. Allergy Asthma Immunol Res. 2021;13(3):420-34. doi: 10.4168/aair.2021.13.3.420.
43. Kang HR, Song HJ, Nam JH, Hong SH, Yang SY, Ju S, et al. Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea. BMJ Open. 2018;8(3):e020825. doi: 10.1136/bmjopen-2017-020825.
44. Meslier N, Charbonneau G, Racineux JL. Wheezes. Eur Respir J. 1995;8(11):1942-8. doi: 10.1183/09031936.95.08111942.
45. Dales RE, Ernst P, Hanley JA, Battista RN, Becklake MR. Prediction of airway reactivity from responses to a standardized respiratory symptom questionnaire. Am Rev Respir Dis. 1987;135(4):817-21. doi: 10.1164/arrd.1987.135.4.817.
46. Tomita K, Sano H, Chiba Y, et al. A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Prim Care Respir J. 2013;22(1):51-8. doi:10.4104/pcrj.2013.00005.
47. Burney PG, Chinn S, Britton JR, Tattersfield AE, Papacosta AO. What symptoms predict the bronchial response to histamine? Evaluation in a community survey of the bronchial symptom questionnaire (1984) of the International Union Against Tuberculosis and Lung Disease. Int J Epidemiol. 1989;18(1):165-73. doi: 10.1093/ije/18.1.165.
48. Mortagy AK, Howell JB, Waters WE. Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma. Br Med J (Clin Res Ed). 1986;293(6546):525-9. doi: 10.1136/bmj.293.6546.525.
49. Barnes PJ, Szefler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: Clinical implications for use of reliever medications. J Allergy Clin Immunol. 2019;144(5):1180-6. doi: 10.1016/j.jaci.2019.06.040.
50. Fuhlbrigge A, Marvel J, Electricwala B, Siddall J, Scott M, Middleton-Dalby C, et al. Physician-Patient Concordance in the Assessment of Asthma Control. J Allergy Clin Immunol Pract. 2021;9(8):3080-8.e1. doi: 10.1016/j.jaip.2021.03.056.
51. Murugesan N, Saxena D, Dileep A, Adrish M, Hanania NA. Update on the Role of FeNO in Asthma Management. Diagnostics (Basel). 2023;13(8):1428. doi: 10.3390/diagnostics13081428.
52. Pesantes E, Hernando R, Lores C, Cámara J, Arévalo E, Lores L. Utility of exhaled nitric oxide to guide mild asthma treatment in atopic patients and its correlation with asthma control test score: a randomized controlled trial. BMC Pulm Med. 2024;24(1):421. doi: 10.1186/s12890-024-03227-y.
53. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3(11):849-58. doi: 10.1016/S2213-2600(15)00367-7.
54. Vedel-Krogh S, Fallgaard Nielsen S, Lange P, Vestbo J, Nordestgaard BG. Association of Blood Eosinophil and Blood Neutrophil Counts with Asthma Exacerbations in the Copenhagen General Population Study. Clin Chem. 2017;63(4):823-32. doi: 10.1373/clinchem.2016.267450.
55. Kole TM, Vanden Berghe E, Kraft M, Vonk JM, Nawijn MC, Siddiqui S, et al. Predictors and associations of the persistent airflow limitation phenotype in asthma: a post-hoc analysis of the ATLANTIS study. Lancet Respir Med. 2023;11(1):55-64. doi: 10.1016/S2213-2600(22)00185-0.
56. Giovannelli J, Chérot-Kornobis N, Hulo S, Ciuchete A, Clément G, Amouyel P, et al. Both exhaled nitric oxide and blood eosinophil count were associated with mild allergic asthma only in non-smokers. Clin Exp Allergy. 2016;46(4):543-54. doi: 10.1111/cea.12669.
57. Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, Pavord I. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. Thorax. 2022;77(2):199-202. doi: 10.1136/thoraxjnl-2021-217325.
58. Nathan RA, Kinsman RA, Spector SL, Horton DJ. Relationship between airways response to allergens and nonspecific bronchial reactivity. J Allergy Clin Immunol. 1979;64(6 Pt 1):491-9. doi: 10.1016/0091-6749(79)90058-7.
59. Muller BA, Leick CA, Smith RM, Suelzer MT, Richerson HB. Comparisons of specific and nonspecific bronchoprovocation in subjects with asthma, rhinitis, and healthy subjects. J Allergy Clin Immunol. 1993;91(3):758-72. doi: 10.1016/0091-6749(93)90196-m.
60. Diamant Z, Gauvreau GM, Cockcroft DW, Boulet LP, Sterk PJ, de Jongh FH, et al. Inhaled allergen bronchoprovocation tests. J Allergy Clin Immunol. 2013;132(5):1045-55.e6. doi: 10.1016/j.jaci.2013.08.023.
61. Benckhuijsen J, van den Bos JW, van Velzen E, de Bruijn R, Aalbers R. Differences in the effect of allergen avoidance on bronchial hyperresponsiveness as measured by methacholine, adenosine 5'-monophosphate, and exercise in asthmatic children. Pediatr Pulmonol. 1996;22(3):147-53. doi: 10.1002/(SICI)1099.
62. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. J Allergy Clin Immunol. 1983;71(4):399-406. doi: 10.1016/0091-6749(83)90069-6.
63. Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. Clin Allergy. 1977;7(6):503-13. doi: 10.1111/j.1365-2222.1977.tb01481.x.
64. Cockcroft DW, Hargreave FE, O'Byrne PM, Boulet LP. Understanding allergic asthma from allergen inhalation tests. Can Respir J. 2007;14(7):414-8. doi: 10.1155/2007/753450.
65. Lam S, Tan F, Chan H, Chan-Yeung M. Relationship between types of asthmatic reaction, nonspecific bronchial reactivity, and specific IgE antibodies in patients with red cedar asthma. J Allergy Clin Immunol. 1983;72(2):134-9. doi: 10.1016/0091-6749(83)90520-1.
66. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, et al. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. Am J Respir Crit Care Med. 2001;163(2):406-12. doi: 10.1164/ajrccm.163.2.9912091.
67. Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: Airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest. 2010;138(2 Suppl):11S-17S. doi: 10.1378/chest.10-0231.
68. Sverrild A, Leadbetter J, Porsbjerg C. The use of the mannitol test as an outcome measure in asthma intervention studies: a review and practical recommendations. Respir Res. 2021;22(1):287. doi: 10.1186/s12931-021-01876-9.
69. Gibbons WJ, Sharma A, Lougheed D, Macklem PT. Detection of excessive bronchoconstriction in asthma. Am J Respir Crit Care Med. 1996;153(2):582-9. doi: 10.1164/ajrccm.153.2.8564102.
70. Lee P, Abisheganaden J, Chee CB, Wang YT. A new asthma severity index: a predictor of near-fatal asthma? Eur Respir J. 2001;18(2):272-8. doi: 10.1183/09031936.01.00074401.
71. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836-44. doi: 10.1164/rccm.200401-033OC.
72. Murphy J, McSharry J, Hynes L, Matthews S, Van Rhoon L, Molloy GJ. Prevalence and predictors of adherence to inhaled corti-

costeroids in young adults (15-30 years) with asthma: a systematic review and meta-analysis. J Asthma. 2021;58(5):683-705. doi: 10.1080/02770903.2020.1711916.
73. Lee LK, Obi E, Paknis B, Kavati A, Chipps B. Asthma control and disease burden in patients with asthma and allergic comorbidities. J Asthma. 2018;55(2):208-19. doi: 10.1080/02770903.2017.1316394.
74. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemière C, Ducharme FM. Assessing adherence to inhaled corticosteroids in asthma patients using an integrated measure based on primary and secondary adherence. Eur J Clin Pharmacol. 2017;73(1):91-97. doi: 10.1007/s00228-016-2139-5
75. Serhal S, Saini B, Bosnic-Anticevich S, Krass I, Wilson F, Armour C. Medication Adherence in a Community Population with Uncontrolled Asthma. Pharmacy (Basel). 2020;8(4):183. doi: 10.3390/pharmacy8040183.
76. Sanchis J, Gich I, Pedersen S; Aerosol Drug Management Improvement Team (ADMIT). Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? Chest. 2016;150(2):394-406. doi: 10.1016/j.chest.2016.03.041.
77. Chrystyn H, van der Palen J, Sharma R, Barnes N, Delafont B, Mahajan A, et al. Device errors in asthma and COPD: systematic literature review and meta-analysis. NPJ Prim Care Respir Med. 2017;27(1):22. doi: 10.1038/s41533-017-0016-z.
78. World Health Organization (WHO). Adherence to long-term therapies: evidence for action; 2003. [2018 October 3].
79. Kvarnström K, Westerholm A, Airaksinen M, Liira H. Factors Contributing to Medication Adherence in Patients with a Chronic Condition: A Scoping Review of Qualitative Research. Pharmaceutics. 2021;13(7):1100. doi: 10.3390/pharmaceutics13071100.
80. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. BMC Pulm Med. 2010;10:1. doi: 10.1186/1471-2466-10-1.
81. Ulrik CS, Backer V, Søes-Petersen U, Lange P, Harving H, Plaschke PP. The patient's perspective: adherence or non-adherence to asthma controller therapy? J Asthma. 2006;43(9):701-4. doi: 10.1080/02770900600925569.
82. Peláez S, Lamontagne AJ, Collin J, Gauthier A, Grad RM, Blais L, et al. Patients 'perspective of barriers and facilitators to talking long term controller medication for asthma: a novel taxonomy. BMC Pulm Med. 2015;15:42. doi: 10.1186/s12890-015-0044-9.
83. Magnoni MS, Latorre M, Bettoncelli G, Sanchez-Herrero MG, Lopez A, Calvo E, et al. Asthma control in primary care: the results of an observational cross-sectional study in Italy and Spain. World Allergy Organ J. 2017;10(1):13. doi: 10.1186/s40413-017-0144-5.
84. Bidad N, Barnes N, Griffiths C, Horne R. Understanding patients' perceptions of asthma control: a qualitative study. Eur Respir J. 2018;51(6):1701346. doi: 10.1183/13993003.01346-2017.
85. Vogelberg C, Brüggenjürgen B, Richter H, Jutel M. Real-World Adherence and Evidence of Subcutaneous and Sublingual Immunotherapy in Grass and Tree Pollen-Induced Allergic Rhinitis and Asthma. Patient Prefer Adherence. 2020;14:817-27. doi: 10.2147/PPA.S242957.
86. Musa F, Al-Ahmad M, Arifhodzic N, Al-Herz W. Compliance with allergen immunotherapy and factors affecting compliance among patients with respiratory allergies. Hum Vaccin Immunother. 2017;13(3):514-7. doi: 10.1080/21645515.2016.1243632.
87. Idrose NS, Lodge CJ, Erbas B, Douglass JA, Bui DS, Dharmage SC. A Review of the Respiratory Health Burden Attributable to Short-Term Exposure to Pollen. Int J Environ Res Public Health. 2022;19(12):7541. doi: 10.3390/ijerph19127541.
88. Comberiati P, Di Cicco ME, D'Elios S, Peroni DG. How Much Asthma Is Atopic in Children? Front Pediatr. 2017;5:122. doi: 10.3389/fped.2017.00122.
89. De Roos AJ, Kenyon CC, Zhao Y, Moore K, Melly S, Hubbard RA, et al. Ambient daily pollen levels in association with asthma exacerbation among children in Philadelphia, Pennsylvania. Environ Int. 2020;145:106138. doi: 10.1016/j.envint.2020.106138.
90. Shrestha SK, Katelaris C, Dharmage SC, Burton P, Vicendese D, Tham R, et al. High ambient levels of grass, weed and other pollen are associated with asthma admissions in children and adolescents: A large 5-year case-crossover study. Clin Exp Allergy. 2018;48(11):1421-8. doi: 10.1111/cea.13225.
91. Shrestha SK, Lambert KA, Erbas B. Ambient pollen concentrations and asthma hospitalization in children and adolescents: a systematic review and meta-analysis. J Asthma. 2021;58(9):1155-68. doi: 10.1080/02770903.2020.1771726.
92. Batra M, Dharmage SC, Newbigin E, Tang M, Abramson MJ, Erbas B, et al. Grass pollen exposure is associated with higher readmission rates for pediatric asthma. Pediatr Allergy Immunol. 2022;33(11):e13880. doi: 10.1111/pai.13880.
93. Lappe BL, Ebelt S, D'Souza RR, Manangan A, Brown C, Saha S, et al. Pollen and asthma morbidity in Atlanta: A 26-year time-series study. Environ Int. 2023;177: doi: 10.1016/j.envint.2023.107998.
94. Erbas B, Jazayeri M, Lambert KA, Katelaris CH, Prendergast LA, Tham R, et al. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: a systematic review and meta-analysis. Allergy. 2018;73(8):1632-41. doi: 10.1111/all.13407.
95. Carlsen HK, Haga SL, Olsson D, Behndig AF, Modig L, Meister K, et al. Birch pollen, air pollution and their interactive effects on airway symptoms and peak expiratory flow in allergic asthma during pollen season – a panel study in Northern and Southern Sweden. Environ Health. 2022;21(1):63. doi: 10.1186/s12940-022-00871-x.
96. Dominguez-Ortega J, Navarro A, Delgado Romero J, Dordal T, Habernau A, Rodríguez M, et al. Pollen-Induced Allergic Asthma and Rhinoconjunctivitis: Differences in Outcome Between Seasonal and Nonseasonal Exposure to Allergens Under Real-Life Conditions (The LANDSCAPE Study). J Investig Allergol Clin Immunol. 2020;30(6):454-6. doi: 10.18176/jiaci.0544.
97. D'Amato G, Vitale C, D'Amato M, Cecchi L, Liccardi G, Molino A, et al. Thunderstorm-related asthma: what happens and why. Clin Exp Allergy. 2016;46(3):390-6. doi: 10.1111/cea.12709.
98. Lee J, Kronborg C, O'Hehir RE, Hew M. Who's at risk of thunderstorm asthma? The ryegrass pollen trifecta and lessons learnt from the Melbourne thunderstorm epidemic. Respir Med. 2017;132:146-8. doi: 10.1016/j.rmed.2017.10.012.
99. Nickovic S, Petković S, Ilić L, Pejanović G, Mijić Z, Huete A, et al. Prediction of airborne pollen and sub-pollen particles for thunderstorm asthma outbreaks assessment. Sci Total Environ. 2023;864:160879. doi: 10.1016/j.scitotenv.2022.160879.
100. GEMA 5.0 Spanish Guideline on the Management of Asthma. Available at: ht4ps://www.gemasma.com/.
101. Agency for Care Effectiveness. Available at: https://www.ace-hta.gov.sg/docs/default-source/acgs/asthma-management-(nov-2020).pdf. Last access date: 07/08/2024.
102. Niimi A, Fukunaga K, Taniguchi M, Nakamura Y, Tagya E, Horiguchi T, et al. Executive summary: Japanese guidelines for adult asthma (JGL) 2021. Allergol Int. 2023;72(2):207-26. doi: 10.1016/j.alit.2023.02.006.

103. Yang CL, Hicks E, Mitchell P, Reisman J, Podgers D, Hayward KM, et al. Canadian Thoracic Society 2021. Guideline update: Diagnosis and management of asthma in preschoolers, children and adults. Can J Respir Crit Care Sleep Med. 2021;5(6):348-61. doi: 10.1080/24745332.2021.194588719.
104. Kim DK, Park YB, Oh YM, Jung KS, Yoo JH, Yoo KH, et al. Steering and Scientific Committee of Asthma Study Group and Guideline Control Committee in The Korean Academy of Tuberculosis and Respiratory Diseases (KATRD). Korean Asthma Guideline 2014: Summary of Major Updates to the Korean Asthma Guideline 2014. Tuberc Respir Dis (Seoul). 2016;79(3):111-20. doi: 10.4046/trd.2016.79.3.111.
105. Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017;389(10065):157-66. doi: 10.1016/S0140-6736(16)31399-X.
106. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy. 2007;62(6):591-604. doi: 10.1111/j.1398-9995.2007.01394.x.
107. Bonsignore MR, Profita M, Gagliardo R, Riccobono L, Chiappara G, Pace E, et al. Advances in asthma pathophysiology: stepping forward from the Maurizio Vignola experience. Eur Respir Rev. 2015;24(135):30-9. doi: 10.1183/09059180.10011114.
108. Profita M, La Grutta S, Carpagnano E, Riccobono L, Di Giorgi R, Bonanno A, et al. Noninvasive methods for the detection of upper and lower airway inflammation in atopic children. J Allergy Clin Immunol. 2006;118(5):1068-74. doi: 10.1016/j.jaci.2006.07.028.
109. Tan DJ, Lodge CJ, Walters E, Lowe AJ, Bui DS, Bowatte G, et al. Biomarkers of asthma relapse and lung function decline in adults with spontaneous asthma remission: a population-based cohort study. Allergy. 2023;78(4):957-967. doi: 10.1111/all.15566.
110. O'Sullivan MJ, Lan B. The Aftermath of Bronchoconstriction. J Eng Sci Med Diagn Ther. 2019;2(1):108031-6. doi: 10.1115/1.4042318.
111. Hill MR, Philp CJ, Billington CK, Tatler AL, Johnson SR, O'Dea RD, Brook BS. A theoretical model of inflammation- and mechanotransduction-driven asthmatic airway remodelling. Biomech Model Mechanobiol. 2018;17(5):1451-70. doi: 10.1007/s10237-018-1037-4.
112. Winkler T. Mechanisms of airway remodeling converge at the critical point of bronchoconstriction in asthma. Ann Transl Med. 2022;10(22):1188. doi: 10.21037/atm-22-5095.
113. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of Bronchoconstriction on Airway Remodeling in Asthma. N Engl J Med. 2011;364(21):2006-15. doi: 10.1056/NEJMoa1014350.
114. Bagley DC, Russell T, Ortiz-Zapater E, Stinson S, Fox K, Redd PF, et al. Bronchoconstriction damages airway epithelia by crowding-induced excess cell extrusion. Science. 2024;384(6691):66. doi: 10.1126/science.adk2758.
115. Latorre M, Pistelli R, Carpagnano GE, Celi A, Puxeddu I, Scichilone N, et al. Symptom *versus* exacerbation control: an evolution in GINA guidelines? Ther Adv Respir Dis. 2023;17:17534666231159261. doi: 10.1177/17534666231159261.
116. Loymans RJ, Gemperli A, Cohen J, Rubinstein SM, Sterk PJ, Reddel HK, et al. Comparative effectiveness of long-term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. BMJ. 2014;348:g3009. doi: 10.1136/bmj.g3009.
117. Chapman KR, Barnes NC, Greening AP, Jones PW, Pedersen S. Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal. Thorax. 2010;65(8):747-52. doi: 10.1136/thx.2009.128504.
118. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006;368:744-53. doi: 10.1016/S0140-6736(06)69284-2.
119. Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med 2013;1: 23–31.
120. Pavord ID, Jeffery PK, Qiu Y, Zhu J, Parker D, Carlsheimer A, et al. Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol. J Allergy Clin Immunol. 2009;123(5):1083-9, 1089.e1-7. doi: 10.1016/j.jaci.2009.02.034.
121. Chapman KR, An L, Bosnic-Anticevich S, Campomanes CM, Espinosa J, Jain P, et al. Asthma patients' and physicians' perspectives on the burden and management of asthma, Respir Med. 2021;186:106524. doi: 10.1016/j.rmed.2021.106524.
122. Chapman KR, Canonica GW, Lavoie KL, Nenasheva N, Garcia G, Bosnic-Anticevich S, et al. Patients' and physicians' perspectives on the burden and management of asthma: Results from the APPaRENT 2 study. Respir Med. 2022;201:106948. doi: 10.1016/j.rmed.2022.106948.
123. Aggarwal B, Al-Moamary M, Allehebi R, Alzaabi A, Al-Ahmad M, Amin M et al. APPaRENT 3: Asthma Patients' and Physicians' Perspectives on the Burden and Management of Asthma in Seven Countries. Adv Ther. 2024;41(8):3089-118. doi: 10.1007/s12325-024-02900-2.
124. Daley-Yates P, Brealey N, Thomas S, Austin D, Shabbir S, Harrison T, et al. Therapeutic index of inhaled corticosteroids in asthma: A dose-response comparison on airway hyperresponsiveness and adrenal axis suppression. Br J Clin Pharmacol. 2021;87(2):483-93. doi: 10.1111/bcp.14406.
125. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA. 2013;309(12):1278-88. doi: 10.1001/jama.2013.2049.
126. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. J Allergy Clin Immunol. 2013;132(6):1322-36. doi: 10.1016/j.jaci.2013.09.004.
127. Fritzsching B, Contoli M, Porsbjerg C, Buchs S, Larsen JR, Elliott L, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: Results from the REACT study, a retrospective cohort study. Lancet Reg Health Eur. 2021;13:100275. doi: 10.1016/j.lanepe.2021.100275.
128. Woehlk C, Von Bülow A, Ghanizada M, Søndergaard MB, Hansen S, Porsbjerg C. Allergen immunotherapy effectively reduces the risk of exacerbations and lower respiratory tract infections in both seasonal and perennial allergic asthma: a nationwide epidemiological study. Eur Respir J. 2022;60(5):2200446. doi: 10.1183/13993003.00446-2022.
129. Demoly P, Molimard M, Bergman JF, Delaisi B, Gouverneur A, Vadel J, et al. Impact of liquid sublingual immunotherapy on asthma onset and progression in patients with allergic rhinitis: a nationwide population-based study (EfficAPSI study). The Lancet Regional Health – Europe. 2024;41:100915. doi: 10.1016/j.lanepe.2024.100915.
130. Pfaar O, Ankermann T, Augustin M, Bubel P, Böing S, Brehler R, et al. Guideline on allergen immunotherapy in IgE-mediated allergic diseases: S2K Guideline of the German Society of Allergology

and Clinical Immunology (DGAKI), Society of Pediatric Allergology and Environmental Medicine (GPA), Medical Association of German Allergologists (AeDA), Austrian Society of Allergology and Immunology (ÖGAI), Swiss Society for Allergology and Immunology (SSAI), German Dermatological Society (DDG), German Society of OtoRhinoLaryngology, Head and Neck Surgery (DGH-NO-KHC), German Society of Pediatrics and Adolescent Medicine (DGKJ), Society of Pediatric Pulmonology (GPP), German Respiratory Society (DGP), German Professional Association of Oto-laryngologists (BVHNO), German Association of Paediatric and Adolescent Care Specialists (BVKJ), Federal Association of Pneumologists, Sleep and Respiratory Physicians (BdP), Professional Association of German Dermatologists (BVDD). Allergol Select. 2022;6:167-232. doi: 10.5414/ALX02331E.

131. Montori VM, Ruissen MM, Hargraves IG, Brito JP, Kunneman M. Shared decision-making as a method of care. BMJ Evid Based Med. 2023;28(4):213-7. doi: 10.1136/bmjebm-2022-112068.
132. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care. 2009;15(6):e22-33.
133. Vaghi A, Incalzi RA, Barbaglia S, Bilò MB, Bini F, Carone M, et al. Expert opinion on gray areas in asthma management: A lesson from the innovative project "revolution in asthma" of the Italian thoracic society (AIPO-ITS). Clin Transl Allergy. 2025;15(2):e70037. doi: 10.1002/clt2.70037.
134. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC); Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol. 2020;146(6):1217-70. doi: 10.1016/j.jaci.2020.10.003.