

Targeted Treatment in Asthma—Opportunities and Challenges



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This review summarizes the key insights and future directions on targeted asthma treatment discussed during the 2025 Expert Meeting supported by the Central and Southern European Allergy and Asthma Alliance (CSEA3). Targeted treatment in asthma is becoming an attainable goal for selected patients but is not yet established as a standard asthma care pathway. The expert panel identified 4 key priorities to advance targeted asthma management: (1) Defining remission—a universally accepted, evidence-based definition is needed to guide clinical practice and guideline development. (2) The management of mild asthma guided by patient stratification according to asthma pathogenetic pathways (endotype) and risk profile may enable more tailored therapy and better outcomes. (3) Biomarker discovery and validation—research must prioritize predictive biomarkers that are easy to measure at the point of care, supported by innovative trials that combine precision immunology and machine learning. (4) Optimizing implementation and addressing the barriers to adopting

stratified care, including limited resources and cost-effectiveness concerns, must be addressed. Digital tools offer promise but require further validation. Coordinated efforts are essential to translate advances in personalized asthma treatment into better outcomes and more sustainable care, particularly in resource-limited settings. © 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2026;14:76-93)

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Despite recent advances and the availability of targeted biologics and small molecules, uncontrolled asthma in real-world settings continues to significantly contribute to morbidity, mortality, and increased health care resource utilization. In

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Abbreviations used

AHR- Airway hyper-responsiveness
AI- Artificial intelligence
AIT- Allergen immunotherapy
BD- Bronchodilator
BM- Basal membrane
BMI- Body mass index
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
CSEA3- Central and Southern European Allergy and Asthma Alliance
DMAD- Disease-modifying antiasthmatic drugs
ECP- Eosinophilic cationic protein
EPX- Eosinophil peroxidase
FeNO- Fractional exhaled nitric oxide
FEOS- FEV1, exacerbations, oral corticosteroids, symptoms
FEV1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
HCP- Health care professionals
ICS- Inhaled corticosteroids
LTRA- Leukotriene-receptor antagonist
OCS- Oral corticosteroids
QoL- Quality of life
RCT- Randomized controlled trial
RWE- Real-world evidence
SABA- Short-acting β_2 -agonist
SNP- Single-nucleotide polymorphism
T2- Type 2 immune response
U-BIOPRED- Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

2007, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort reported 83% patients with uncontrolled asthma, and in 2023, the NOVEL observational longitudinal study (NOVELTY) reported uncontrolled asthma still as high as 69%, irrespective of the type 2 immune response (T2) inflammation biomarkers.^{1,2} Although conventional asthma controllers are effective for most patients with mild-to-moderate asthma, many still experience severe, life-threatening exacerbations and have a markedly reduced quality of life (QoL). Biologic therapies play a crucial role in reducing exacerbations, hospitalizations, and the need for maintenance systemic steroids, while also improving QoL in patients with severe asthma. However, real-world responder rates rarely exceed 50%. Similarly, although most children receiving biologics achieve good symptom control, many still experience asthma attacks.³ Moreover, focusing solely on disease severity significantly underestimates the overall asthma burden: in the Severe Asthma Research Program III (SARP III) and Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) studies, 28% and 27% of participants with nonsevere asthma, respectively, had burden scores above the median.⁴

A key challenge in asthma research is translating emerging insights into diverse pathobiological mechanisms (disease endotype) that guide targeted, patient-specific therapies, ultimately aiming to modify the disease's natural course. Efforts should therefore focus on converting discoveries in asthma pathogenesis and targeted treatments into sustainable point-of-care management algorithms and transformative health care policies. Achieving this requires

aligning research and management strategies with the priorities of end users: patients, carers, and clinicians.

Targeted treatment in asthma is becoming an achievable goal for selected patients but has not yet been established as a standard care pathway. The Global Initiative for Asthma emphasizes a personalized treatment approach, which includes a 2-track strategy for mild asthma and tailored plans for more severe or difficult-to-control cases. These plans consider factors such as the patient's symptoms, risk of exacerbations, medication access and cost, inhaler technique, likely adherence, and underlying endotypes. Currently, asthma remission is not included as a formal management goal.⁵

In March 2025, the Central and Southern European Allergy and Asthma Alliance (CSEA3) organized a think tank on targeted asthma management in Krakow, Poland. The expert panel identified 4 key priorities to advance targeted asthma management. This review summarizes the 4 key points discussed during the event: (1) What is asthma remission, and how can it be achieved? (2) Is targeted treatment recommended for mild asthma? (3) What can be done at the point of care? (4) Is targeted asthma treatment sustainable? (Box 1)

WHAT IS ASTHMA REMISSION AND HOW IT CAN BE ACHIEVED?

Over the past 2 decades, highly effective disease-modifying antiasthmatic drugs (DMAD) with remarkable safety and beneficial effects on asthma comorbidities, such as allergen immunotherapy (AIT) and biologics, have been introduced and led to a paradigm shift in asthma toward the concept of disease modification.⁶

With the advent of asthma biologics and the recognition of "super responders," the focus in asthma management has shifted from control to remission as a realistic treatment goal in daily practice.⁷ It is estimated that approximately 20% to 40% of patients receiving biologics could achieve "on-treatment" remission based on predefined criteria.⁸ Defining remission as an attainable goal allows clinicians to consider reducing background or biologic therapy, while optimizing long-term management through stabilized lung function and a sustained absence of symptoms, often evaluated over a year. The concept of remission in asthma provides an ambitious target and asthma management outcome (Figure 1). However, it is debatable whether it brings more clarity on the natural evolution of the disease and, more importantly, whether it will manage to reduce the current asthma burden.⁹

How is asthma remission defined?

Asthma remission refers to a state in which an individual with asthma experiences no significant symptoms, requires no controller medications, and shows no signs of functional or inflammatory disease activity. Unlike a cure, remission is temporary, although it might be long-term.

Depending on the target asthma, remission can be categorized into the following:¹⁰

- (1) Clinical remission: most frequently defined via the FEOS score (forced expiratory volume in 1 second [FEV1], exacerbations, oral corticosteroids [OCS], symptoms), with or without ongoing treatment.
- (2) Biological remission: no airway hyper-responsiveness (AHR), absence of type 2 inflammation (eg, normal

Box 1. Defining the key concepts for personalized asthma management

Phenotype	Refers to the observable characteristics or visible traits of a disease, such as clinical presentation and triggers, inflammatory or molecular pattern, which arise due to interactions between the genome and the environment	Although phenotypes provide valuable clinical insights, they may not fully capture the underlying pathophysiological processes Patients with similar phenotypes may have fundamentally different pathophysiological pathways, necessitating different therapeutic approaches
Endotype	Disease subtypes based on distinct functional or pathobiological mechanism	One of the best examples is type 2 asthma, a complex endotype characterized by eosinophilic inflammation and responsiveness to specific biologics targeting the IL-4/IL-13, IL-5, or IgE-driven pathogenetic pathways Disease endotypes are not fixed entities as they can shift in the same patient after environmental exposure
Regiotype	Concept introduced to account for regional variations in disease expression, influenced by environmental factors, lifestyle, and/or allergen exposures	Acknowledges that geographic and environmental contexts can modulate disease mechanisms
Theratype	Prediction of response to targeted intervention based on the pathogenetic pathways	Particularly impactful in managing severe asthma, where biologics are chosen based on the patient's specific endotypic profile
Biomarker	Measurable indicator linking the disease phenotype to the disease endotype	Can be further classified as diagnostic, prognostic, predictive, or monitoring
Targeted treatment	Treatment selection based on major pathogenetic pathways	Current approach for patients with severe asthma receiving biologics or novel small molecules
Stratified medicine	Classification of individuals into subgroups based on their risk of developing a disease or a complication of a disease or based on response to a targeted intervention	Several stratified approaches were implemented over time for managing asthma based on steroid responsiveness, eosinophilic inflammation, etc.
Remission	State in which an individual with asthma experiences no significant symptoms, requires no controller medications, and shows no signs of functional or inflammatory disease activity	A standardized definition has not yet been achieved
Future risk	Tracking a patient's health and outcomes over an extended period to manage their condition effectively	Particularly relevant for asthma is the risk of exacerbations, lung function growth, lung function decline, and treatment-related adverse events

eosinophil count and fractional exhaled nitric oxide [FeNO]), no remodeling.

- (3) Complete remission: proposed term when both clinical and biological remission criteria met.

For the definition of clinical remission, the FEOS score was proposed, comprising lack of symptoms, improvement in lung function, and lack of use of OCS and of severe exacerbations.¹¹ Clinical remission is a multicomponent aspirational term but not very different from perfect asthma control, except for longer duration (at least 12 months). The difference from control is that one of the criteria is not requiring OCS.

A recent systematic review evaluated definitions of asthma clinical remission, including 25 studies that reported 28 analyses of remission attainment. The review identified 68 definitions of clinical remission, of which 48 were unique.¹² Eight analyses applied a 3-component definition, whereas 25 used a 4-component definition. Overall, there was little consensus across studies, particularly regarding criteria for symptoms and lung function. The pooled proportion of patients achieving clinical remission was 38% (95% confidence interval [CI], 29%-47%; $I^2 = 93\%$) for the 3-component definition and 30% (95% CI, 27%-34%; $I^2 = 83\%$) for the 4-component definition.

Biological remission implies a fundamental alteration of asthma trajectory such that treatment can be significantly scaled back or even eliminated altogether, in a subject who is not exacerbating, minimally symptomatic, and has stable lung function. To achieve this, the intervention needs to block reinforcing positive feedback loops between pathologic airway inflammation and alterations in airway structure that perpetuate the asthmatic disease state. Although we have a reasonably good understanding of and treatment for pathologic airway inflammation, our ability to diagnose and treat the perturbed airway structure in asthma needs more attention, ideally by using noninvasive techniques. Airway structure encompasses both established pathologic changes (eg, airway smooth muscle mass or altered mucus) and more subtle molecular pathology (eg, epithelial barrier dysfunction). Recent studies using design-based stereology showed that basal membrane (BM) thickening was associated with bronchodilator (BD) reversibility, demonstrating that we still do not fully understand the relationship between airway pathology and disease pathophysiology.¹³

Given the heterogeneity of asthma and its natural history, which is not yet fully understood, the definition of complete remission has not yet been validated.

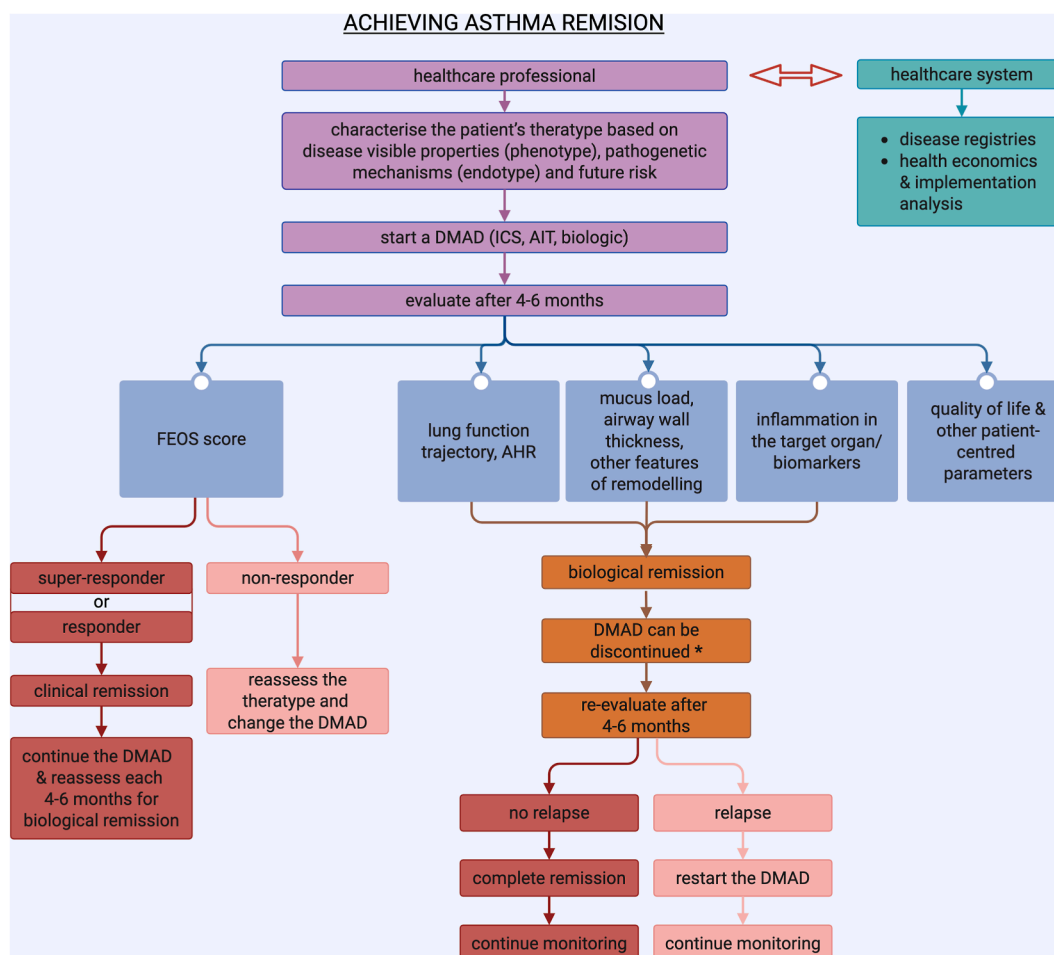


FIGURE 1. Achieving asthma remission as a goal for asthma management. The health care professional should assess in depth the theratype (prediction of response to treatment) based on visible properties (asthma severity, age at onset, comorbidities, and triggers), disease mechanisms (T1, T2, and T3 immune response and related biomarkers; allergen-driven, etc), and future risk (exacerbations, lung function decline, and medication-related adverse events) and start the appropriate DMAD (ICS, AIT, and biologic). After 4 to 6 months, the FEOS score (FEV1, exacerbations, oral corticosteroids, and symptoms) can be used to decide on the responder status. If the patient is a super-responder or a responder, clinical remission is achieved, and the DMAD should be continued with periodical monitoring for the biological remission monitoring parameters. If the lung function trajectory is stable and remodeling and inflammation recede, biological remission is achieved, and the DMAD can be discontinued with regular monitoring for relapse*. If no relapse is seen after 4 to 6 months, complete remission is achieved, and monitoring should continue for a late relapse. In case of relapse, the DMAD should be reinstalled. If the patient is a nonresponder according to the FEOS score, the theratype should be reassessed to decide on the change of the DMAD. *This recommendation is based on expert opinion, as no clinical trial evidence currently supports discontinuation of DMAD after achieving biological remission. It reflects practices in other conditions managed with disease-modifying agents (such as rheumatoid arthritis, psoriasis, and Crohn disease), where therapy is often withdrawn once remission is achieved, and patients are monitored for relapse. The panel also considered the high costs and potential cumulative toxicity associated with continuing DMAD in patients who have already achieved remission. Although a majority of panelists supported this recommendation, there was no unanimous agreement. Being based on expert opinion, it is intended to guide but not mandate clinical decision-making. *AHR*, Airway hyper-responsiveness; *AIT*, allergen immunotherapy; *DMAD*, disease-modifying antiasthmatic drugs; *FEV1*, forced expiratory volume in 1 second; *FEOS*, FEV1, exacerbations, oral corticosteroids, symptoms; *ICS*, inhaled corticosteroids, *T1/2/3*, type 1, 2, 3 immune response.

Depending on the means for achieving remission, asthma remission can be:

1. Spontaneous remission (eg, childhood asthma)
2. Remission "on treatment" by using DMAD (inhaled corticosteroids [ICS] or biologic therapy)
3. Remission "off treatment" (eg, after successful AIT).

The importance of understanding spontaneous asthma remission

A key area in understanding asthma remission is defining treatment-induced remission compared with spontaneous asthma remission. Understanding spontaneous asthma remission and its predictors might guide the treat to target

intervention with highly effective DMAD, similar to the study of AIT mechanisms of action versus natural models of immune tolerance, such as the beekeepers.^{14,15}

Spontaneous remission is possible as part of the natural history of asthma. It is more common in childhood. The natural course of childhood asthma, after its onset, is characterized by periods of persistence, relapse, and remission. Over the 10 years of follow-up, the rate of asthma remission was 37 per 100 person-years. Early-onset asthma and being female and living in a rural and medium-urban location were positively associated with remission, whereas a history of atopy decreased the likelihood of remission.¹⁶ Moreover, in a longitudinal analysis of a well-characterized cohort, half of the children with severe asthma no longer had severe asthma after 3 years. Asthma severity decreased equally in male and female subjects, and peripheral eosinophilia predicted resolution.¹⁷ Although they have similar pathogenetic features, patients with nonatopic asthma tend to have milder symptoms of asthma and typically outgrow their asthma by adolescence.¹⁸ Neutrophilic airway inflammation was reported for this phenotype.¹⁹ The Tucson Children's Respiratory Study was the first longitudinal assessment of the natural history of asthma in which children were enrolled at birth and provided valuable clues about the most important risk factors for and the prognosis of different phenotypes associated with recurrent airway obstruction during childhood. Atopy was associated with persistent asthma and with significant deficits in lung function growth up to age 11 years.²⁰

The prevalence of spontaneous remission in the adult asthma population varies between 2% and 52%, depending on the various definitions used. The factors associated with remission include mild asthma, better lung function, better asthma control, younger age, early-onset asthma, shorter duration of asthma, milder AHR, fewer comorbidities, and smoking cessation or never smoking.²¹ Participants from the Tasmanian Longitudinal Health Study with spontaneous asthma remission at ages 45 (n = 466) and 50 (n = 318) years were re-evaluated at age 53 for associations between baseline inflammatory biomarkers and subsequent asthma relapse and lung function decline. Three cytokine profiles were identified: average (34%), T2-high (42%), and T2-low (24%). Compared with the average profile, a T2-high profile was associated with accelerated decline in post-BD FEV1/forced vital capacity (FVC), whereas a T2-low profile was associated with accelerated decline in both post-BD FEV1 and post-BD FVC. AHR and high TNF- α during spontaneous remission were associated with an increased risk of asthma relapse. No evidence of association between exhaled breath condensate nitrogen oxides and either asthma relapse or lung function decline was observed. These findings suggest a closer monitoring for individuals with AHR, T2-high, or T2-low cytokine profiles.²² By using a strict remission phenotype, 3 single nucleotide polymorphisms (SNPs) were found to be associated with complete asthma remission, where 2 SNPs were found to have an impact on the expression of fibroblast growth factor receptor substrate 2 and chaperone-containing polypeptide, both of which control cellular proliferation, whereas another was associated with the expression of IL-1RL1, IL-18R1, and IL-13.²³

Ways to achieve asthma clinical remission

Current clinical trials and real-world data suggest that all 4 criteria for clinical remission can be maintained for 2 years in

only approximately 35% to 40% of patients.^{12,24-26} There are several limitations to be noted here questioning the reliability of all retrospective findings: persistence over 12 months of items such as improved lung function and asthma control is only tested once (at 52 weeks) and rarely more than twice, thus missing the evidence of persistence over 12 months.

The reason is not that good drugs are not available but that treatment decisions are made based on just 2 biomarkers available at the point of care: blood eosinophils and FeNO. Of note, blood eosinophils are good for assessing the systemic T2 burden, whereas FeNO is a marker of airway inflammation and not of eosinophilic inflammation specifically.²⁷

Furthermore, clinical remission is at best achieved in no more than 30% of patients in most reported cohorts.^{28,29} Remission is more likely achieved in T2-high biomarker patients with shorter duration of disease and less comorbidity.³⁰ The odds of achieving 4-domain remission decreased by 15% for every additional 10 years of asthma duration and increased in those with fewer exacerbations per year, lower OCS daily dose, better control, and better lung function before biologic initiation.³¹ A recent monocentric study reported achieving 3 of the FEOS criteria in 66% of moderate-to-severe asthmatics and 61% when lung function decline was not included. The study shows how broad is individual pathobiology of these conditions and that a comprehensive strategy should be used, not limited to the simplistic collection of predefined clinical data and T2 biomarkers. Only a proactive (rather than a standard 4-5 fixed items) strategy allows tailored management of these conditions. The results were achieved through a 24-month comprehensive, individualized treatment strategy involving the use of anti-inflammatory therapy, biologics, antibiotics, immunomodulators, and bronchial thermoplasty, guided by clinical assessment, airway physiology, sputum inflammometry, and airway imaging. The study proved that if clinical remission is to be achieved in a greater proportion of patients using the currently available treatment modalities, then precision medicine needs to be practiced with the right biomarkers, such as a combination of routine tests such as blood eosinophils, FeNO, sputum cytometry with "research tools" such as sputum cytokines and auto-antibodies, and airway imaging. In this study, 20.2% of patients had immunodeficiencies leading to airway infections that contributed to asthma exacerbations and were treated with antibiotics, hypertonic saline, and/or immunoglobulins, whereas in 9% of patients, symptoms were driven by AHR, and thus they received bronchial thermoplasty guided by functional magnetic resonance imaging after the inflammatory component was controlled.³²

Longitudinal evaluation remains key in evaluating asthma remission. The Danish Severe Asthma Register identified 3 prebiologic disease trajectories with increased disease duration and activity associated with asthma and comorbidity burden: "chronic severe asthma," "gradual onset severe asthma," and "recent, sudden onset severe asthma."³³ The "chronic severe asthma" cluster demonstrated the lowest prevalence of remission (17%) compared with the "gradual onset severe asthma" (29%) and "recent, sudden onset severe asthma" (32%) clusters. The Australian Mepolizumab Registry identified 3 trajectory response groups: "responsive asthma with less OCS use," "responsive late-onset asthma," and "obstructed and less responsive asthma." Groups 1 and 2 demonstrated higher proportions achieving clinical remission. Looking into the airway

cytokines and antibodies and markers can explain the 3 trajectories.^{34,35}

One important point pertaining to disease remission relates to the recent concept of lung function trajectory.³⁶ There is a growing appreciation that both asthma and chronic obstructive pulmonary disease (COPD) evolve with different lung function trajectories.³⁷ For subjects who did not attain maximal predicted airway or lung size, we may never be able to achieve “normal” lung function when compared with group means of healthy nonsmokers. For this reason, focusing on normal lung function as a criterion for disease remission may be misleading. For this purpose, it is worth considering emerging ways to study lung function, such as oscillometry or dynamic imaging.

Another emerging concept relevant for clinical remission is “asthma at risk.” Exacerbations, severe AHR, excessive T2-related biomarkers, noxious environments and patient behaviors, harms of oral OCS and high-doses of ICS, and low adherence-to-effectiveness ratios of ICS-containing inhalers are predictors of future risks. New tools such as imaging, genetic, and epigenetic signatures should be used. Logical and numerical artificial intelligence (AI) may be used to generate a consistent risk score.³⁸

Ways to achieve asthma biological remission

In clinical remission, airway inflammation and remodeling are ongoing. Patients with asthma in clinical remission and patients with clinically active asthma and slow FEV1 decline had a similar extent of airway inflammation and remodeling in sputum and bronchial biopsies.³⁹ Patients with asthma and a fast FEV1 decline had high sputum eosinophil numbers and eosinophil cationic protein (ECP) levels. Basement membrane thickness correlated with sputum eosinophils, sputum ECP, and airway wall eosinophil numbers. BM thickness was reported to be similar in individuals with asthma with complete remission, clinical, and current asthma without ICS.⁴⁰ Stopping the biologic leads to a bounce-back in asthma exacerbations.^{41,42} A dose-titration algorithm of biologics in patients who had achieved clinical control was recently described.⁴³ Although 78% of patients tolerated down-titration of treatment compared with the control arm, the down-titration arm tended to have more exacerbations. Furthermore, there are significant challenges in validating what to monitor during the down-titration: blood eosinophils, symptoms, lung function, and exacerbations.⁴⁴

Biological remission off treatment is achievable in only a very small proportion of asthmatics. No biologic has demonstrated this. This can probably only be achieved in children, in patients with mild asthma, by allergen avoidance (eg, occupational asthma), or with AIT. However, in preschool children at high risk for asthma, 2 years of ICS did not change the development of asthma symptoms or lung function during a third, treatment-free year; thus a disease-modifying effect of ICS after the treatment is discontinued cannot be claimed.⁴⁵ Finally, most of the studies of remission and biologics suggest that one of the predictors of poor response is late initiation of the biologic, suggesting that early initiation might lead to better efficacy. This is likely true but remains to be proven in good studies.

AIT is a disease-modifying intervention that has the potential to achieve biological asthma remission.⁴⁶⁻⁴⁸ AIT is prescribed both to prevent the development of asthma and to treat existing allergic asthma.^{49,50} Several real-world studies have shown that

AIT in patients with allergic rhinitis leads to a significant reduction in the risk of asthma development.⁵¹⁻⁵³ A recent meta-analysis of a total of 17 relevant studies (14,126 patients treated with AIT vs 257,622 untreated controls) showed an average asthma risk reduction of 25% with AIT, with the strongest effects when starting AIT in childhood, in the presence of monosensitization, and with AIT duration over 3 years.⁵⁴ Several randomized controlled trials (RCTs),⁵⁵⁻⁵⁷ real-world evidence (RWE),^{58,59} and metaanalysis⁶⁰ showed a robust impact of AIT on asthma exacerbations and asthma control, while allowing a reduction in the asthma controller medication. Consequently, international guidelines recommend AIT for carefully selected patients with allergic asthma.^{49,61} More recently, there was evidence on restoring the antiviral response of the respiratory epithelium, reducing the epithelial-derived cytokines, and decreasing remodeling.^{62,63} Furthermore, in a few landmark trials of AIT added to biologics (omalizumab, dupilumab, or tezepelumab), mechanisms were also studied, unveiling the additional benefit of these combinations in enhancing not only safety and tolerability, but possibly also efficacy.⁴⁸ In a small prospective study after 1 year of AIT, asthma control achieved on treatment remained stable after 3 and 5 years of AIT, without significant differences in BD and anti-inflammatory therapy.⁶⁴ However, there are no longitudinal data on the long-lasting off treatment potential of AIT in asthma, similar to the studies in allergic rhinitis.⁶⁵

Concluding remarks and open questions

Overall, the concept of remission is a good catalyst for health care professionals (HCP) to aim high in the management of their patients with asthma. Consequently, when evaluating the response to DMAD (biologics or AIT), clinicians should routinely assess now the exacerbation rate, patients' QoL, the improvement in lung function and/or decrease in mucus load, the decrease in remodeling, and the decrease in the need for ICS as maintenance therapy (Figure 1).^{25,66-68}

Several open questions and unmet needs remain: how to optimally define remission, how to identify patients who can achieve it, the timing (window of opportunity) and the duration of the intervention during the course of asthma to achieve remission, how to best tailor the intervention to a particular endotype, and what can be done to achieve biological or complete remission if the patient is a responder to the DMAD. Addressing these questions in asthma will not only refine patient care in this disease but also generate valuable insights for other chronic lung conditions, such as COPD, where defining remission and developing endotype-driven, disease-modifying therapies represent equally pressing challenges (Box 2).

IS TARGETED TREATMENT RECOMMENDED FOR MILD ASTHMA?

What is mild asthma, and why does it represent an unmet need?

A working definition for mild asthma was recently proposed by the American Thoracic Society: mild asthma is asthma that is characterized by minimal symptoms and risk in patients on short-acting β_2 -agonist (SABA) alone, as-needed ICS with SABA, as-needed ICS-formoterol, or daily ICS plus SABA, or those who are not on any therapy.⁶⁹

Box 2. Key points for research and clinical practice for achieving asthma remission

- (1) To further advance the concept of asthma remission, a deeper understanding of asthma's natural history, including its prenatal and early-life origins, the role of the microbiome, immune and inflammatory pathways, and structural changes in the lungs, is urgently needed. This can be facilitated by a multifactorial research approach incorporating deep phenotyping and advanced analytical tools.
- (2) Aiming for asthma remission on treatment (clinical remission) is an achievable goal in the clinic for patients treated with disease-modifying drugs such as inhaled corticosteroids, biologics, or AIT, but different tools should be implemented in the daily practice routine such as assessing the exacerbation rate, patients' quality of life, lung function trajectories, the oral corticosteroid load, or the burden score.
- (3) Biological remission off treatment is achievable only in a very small proportion of asthmatics. It may become a treatment goal in children or in patients with mild asthma, occupational asthma, or with AIT and by using a targeted approach based on disease endotypes.

AIT, Allergen immunotherapy.

Mild asthma accounts for 50% to 75% of patients with asthma. It is typically associated with infrequent symptoms and minor burden on the health care system; thus it is less seen in an asthma clinic and usually managed by primary care or connected specialties.⁷⁰ Most cohorts from childhood to adulthood show that asthma severity usually remains stable over time. It was reported that 3% to 20% may progress to severe asthma, although it is possible that the initial clinical assessment of asthma severity was incorrect.⁷¹ Furthermore, disease progression in patients with seasonal asthma and those followed exclusively by primary care providers is largely unknown.

Although generally considered a benign condition, patients with mild asthma can experience an underappreciated exacerbation burden, which places them at increased risk for accelerated lung function decline and OCS exposure with associated adverse events. Mild asthma is more frequent, more symptomatic, and less well controlled in children than in adults. Furthermore, mild asthma can lead to severe exacerbations, with a frequency ranging from 0.12 to 0.77 per patient-year. Severe exacerbations in mild asthma represent 30% to 40% of asthma exacerbations requiring emergency consultation.⁷⁰ Importantly, 30% to 37% of acute asthma episodes, 16% of near-fatal asthma episodes, and 15% to 27% of fatal attacks occurred in patients reporting symptoms less than weekly or only with exertion in the preceding 3 months.⁷² In clinical trials, rates of severe exacerbations in patients with mild asthma range from 0.20 to 2.88 per year.⁷³ This unexpected disease burden reflects both the lack of a clinically meaningful definition for truly mild asthma and the incomplete understanding of the pathogenetic pathways.^{69,74}

Inflammation and structural remodeling are constant, of varying intensity, but nonspecific. The phenotype of inflammation is not well investigated as patients with mild asthma rarely reach a specialized asthma center. Moreover, although eosinophilic inflammation is common in mild asthma, this may

differ on the basis of clinical characteristics, comorbid disease, ICS dose, and differing environmental factors such as air pollution and allergens or endotoxins.⁷⁵ Based on the high proportion of the allergic patients with mild asthma, the inflammation is usually assumed to be primarily driven by a T2 immune response, with the contribution of AHR and structural remodeling to the symptoms largely neglected. Ideally, patients with mild asthma should be evaluated using a multidimensional approach that includes symptom burden, exacerbation patterns, airway inflammation, AHR, lung function trajectories, and response to treatment. Whether this approach is sustainable and applicable at the point of care remains to be further proven.

Current management of mild asthma

All asthma guidelines recommend that low-dose ICS therapy be initiated early after asthma diagnosis, while patients' symptoms are mild, to prevent deterioration of their condition. For most patients, symptom control is achievable with low-dose ICS or ICS-formoterol as needed, which are both effective and safe. Based on solid evidence, the ICS-formoterol as-needed approach was recently advanced as first-line treatment by all major guidelines to ensure that ICS are given when the patient is symptomatic instead of a SABA only, thus preventing SABA overuse and side effects and the risk of future exacerbations.^{61,76-80} Findings from the PRACTICAL study showed that most patients preferred as-needed corticosteroid-formoterol therapy if they had experienced it.⁸¹ Recently, as-needed use of albuterol-budesonide was shown to lower the risk of a severe asthma exacerbation compared with as-needed use of albuterol in patients uncontrolled despite treatment for mild asthma with a SABA with or without a low-dose ICS or leukotriene-receptor antagonist (LTRA).⁸²

Toward "treat to target" in mild asthma

ICS decreases eosinophilic inflammation but has only a slight effect on AHR and on structural remodeling, and, when stopped, inflammation immediately recurs.^{83,84} Consequently, long-term low-dose ICS (daily or intermittent and symptom-driven) is recommended, with a significant impact on adherence to treatment and on future risk due to the cumulative ICS dose, especially in the pediatric population.⁸⁵ Furthermore, the adherence rates to ICS are particularly low in mild asthma, with up to 50% patients reported having low and medium adherence.⁸⁶

There are several arguments in favor of the "treat-to-target" approach guided by disease endotypes and theratypes for particular mild asthma phenotypes to (1) improve treatment response, (2) minimize future risk in patients prone to severe exacerbations or with fast lung function decline, and (3) achieve biological remission, currently not reached with ICS or other asthma controllers.⁸⁷ Prediction of future risk is however difficult. Frequent exacerbations were related to increased risk of accelerated lung function decline; however, further research is required to elucidate the link between lung function decline and less frequent exacerbations, as may be experienced by many people with mild asthma.^{88,89} Furthermore, as the OCS prescription threshold is higher in mild asthma, future research on mild asthma also requires a reproducible definition of exacerbations.⁶⁹ Small airways disease, T2 biomarkers, and comorbidities have also been suggested as prognostic for future risk.⁹⁰⁻⁹³ The additional burden of environmental factors

(smoking—which might also impact the response to ICS—exposure to allergens, indoor or outdoor pollutants, climate change, poor nutrition, and chronic stress) or gender and race must be accounted for in calculating the future risk, together with societal factors such as lack of access to proper diagnosis or to essential medications.⁹⁴⁻¹⁰²

Can mild asthma management be guided by T2 biomarkers?

Although theoretically plausible, T2 biomarker-guided therapy (FeNO and sputum eosinophils), by and large, has not been unequivocally proven to be advantageous over clinically guided therapy in mild asthma. The Best Adjustment Strategy for Asthma in the Long-Term (BASALT) study was one of the largest studies to demonstrate this.¹⁰³ One exception was the Managing Asthma in Pregnancy (MAP) trial, which showed that asthma exacerbations during pregnancy can be significantly reduced with a validated FeNO-based treatment algorithm, with its Growing into Asthma double-blind follow-up study showing a significant decrease in the new-onset asthma in the offspring.^{104,105} Gradual ICS reduction when FeNO is <50 parts per billion may help decrease ICS use without increasing exacerbations.¹⁰⁶ Of note, in untreated mild persistent asthma, there is substantial discordance between sputum eosinophilia, blood eosinophil count, and FeNO.¹⁰⁷ In another trial, children with a parental history of asthma, increased FeNO levels, low provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) values, or a history of ICS use had the best long-term outcomes with ICS therapy compared with treatment with LTRA.¹⁰⁸ However, a more recent trial failed to show any significant outcomes using FeNO-guided asthma pharmacotherapy in asthma; thus, more research is needed in this area.¹⁰⁹ Another trial showing a benefit of blood eosinophil-guided strategy was the Novel-START study, showing that the benefits of maintenance inhaled budesonide are greater in patients with high blood eosinophil counts than in patients with low counts.¹¹⁰ In conclusion, there might be a small subset of patients with mild asthma who might benefit from T2 biomarker-driven strategies; however, at a population level, this may not be necessary or cost-effective, and other approaches exploring composite endpoints including T2 biomarkers or multidimensional endotypes based on noninvasive biomarkers from the nose or from the skin barrier might be considered.^{111,112}

Concluding remarks and open questions

In conclusion, mild asthma should be further coined as “mild asthma syndrome” depicting a heterogeneous population with different pathogenetic pathways, response to treatment, and future risk (Figure 2).

Based on the current evidence, for a minimally symptomatic patient with baseline normal lung function, no lung function decline, and infrequent mild exacerbations, low- to medium-dose ICS + long-acting β_2 -agonist/SABA as per current guidelines is probably enough. However, high levels of T2 biomarkers (eg, FeNO, blood eosinophils, or sputum cell counts—“magnet driven” and “bomb driven” asthma)¹¹⁰ or a frequent exacerbator phenotype should prompt to change the management of the mild asthmatic, at least with more careful monitoring of adherence to treatment and to environmental measures, educational programs, and proper use of medications

along with a skilled approach, together with a caring attitude of health care providers.⁹²

Lung function trajectories would also be useful here because mild asthma in a patient with low or declining lung function should probably be treated more intensively and in a more targeted manner than a subject with normal range and stable lung function. Educational effort should be directed toward specialists and general practitioners to increase awareness regarding these patients. Furthermore, treatment should be optimized based on what is causing the symptoms—inflammation, AHR, abnormal mucus production, and/or extensive remodeling.⁸⁷

Aiming for biological remission in mild asthma should be reinforced, as this has the best chance of success. In a study of patients with mild allergic asthma undergoing inhaled allergen challenge, a single dose of tezepelumab normalized baseline blood and sputum eosinophils and FeNO and significantly diminished AHR.¹¹³ Anti-T2-targeted treatment (IgE, IL-4/IL-13, and IL-5) might also be of interest given the large population of T2 mild asthmatics.^{87,114,115} However, the use for expensive “biologics” in a selected mild asthma population needs to be determined in properly designed longitudinal studies focused on economic efficiency. Until then, AIT remains a key tool for a personalized approach in patients with mild allergic asthma, aiming to decrease the disease burden and improve the long-term outcomes (Box 3).^{46,49,50,116}

WHAT CAN BE DONE AT THE POINT OF CARE FOR IMPLEMENTING TARGETED APPROACHES IN ASTHMA?

The goals of asthma management at the point of care are to achieve optimal symptom control, minimize the risk of future exacerbations and lung function decline, maximize treatment effectiveness, reduce medication-related adverse events, improve patient QoL, and ultimately achieve asthma remission. This requires an adequate assessment of the individual profile of each patient with asthma and its comorbidities based on disease mechanisms predicting response to treatment (theratype) together with disease future risk (Figure 2). Furthermore, patients (and/or caregivers) should engage in shared decision-making with HCP and develop adequate management and monitoring plan centered on the balance between necessity (symptom control, QoL, and disease remission) and concern (side effects and cost of medication, socioeconomic status, lifestyle changes, and environmental control) (Figure 3).¹¹⁷ The partnership between the patients/caregivers and health care providers is important in ensuring the success of the management. However, implementation and sustainability for the health care system remain significant barriers in reaching these goals.

Stratified asthma management based on biomarkers

Biomarkers are key to defining asthma phenotypes, although they should not be used in isolation from clinical characteristics, including age, age of asthma onset, and the presence of comorbidities and various environmental triggers. In the decision-making process, they should be integrated with the assessment of future risk (exacerbation-prone or fast lung function decline) and the suboptimal response to treatment

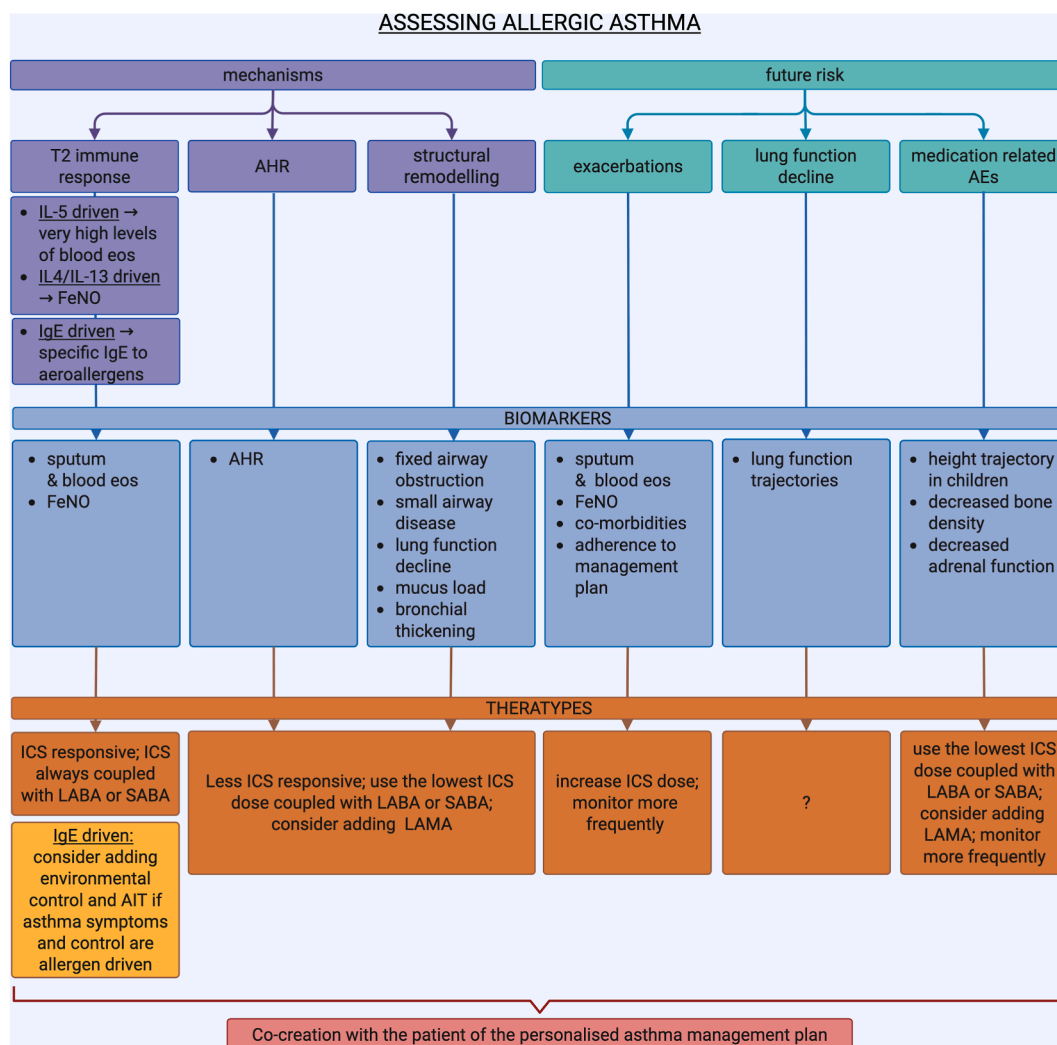


FIGURE 2. Management of the mild asthma syndrome—a continuum from the point of care to the specialized asthma center. Asthma diagnosis should include the assessment of its major pathogenetic mechanisms (T2 immune response, AHR, and structural remodeling), together with the evaluation of future risk (exacerbations, lung function decline, or medication-related adverse events). Easy to measure at the point of care, noninvasive biomarkers should be used, such as FeNO and blood eosinophils for T2 immune response, AHR, lung function, height trajectories, and the presence of comorbidities. In more specialized settings, mucus load, bronchial thickening, or special measurements in sputum or nasal secretions (antibodies, proteomics, and transcriptomics), bone density, or adrenal function measurements can be added. This added value of this stratified approach is to guide the therapeutic decision (theratype) to maximize the efficacy and safety of the intervention. *AE*, Adverse events; *AHR*, airway hyper-responsiveness; *AIT*, allergen immunotherapy; *eos*, eosinophils; *FeNO*, fractional exhaled nitric oxide; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist; *LAMA*, long-acting muscarinic antagonist; *SABA*, short-acting β_2 -agonist; *T2*, type 2 immune response.

(incorrect identification of the specific T2 pathways, autoimmune phenomena, infections, changes in the initial inflammatory phenotype, insufficient treatment dose, and adverse events caused by asthma medications). They also need further analytical and clinical validation and qualification.¹¹⁸ To date, no asthma biomarker has been evaluated in a prospectively collected cohort of the target population using the rigorous “prospective-specimen-collection, retrospective-blinded-evaluation” design. Furthermore, the intended use of each biomarker—such as for risk stratification or predicting treatment response—needs to be clearly defined.

FeNO and blood eosinophils are the only 2 tests that are currently easily accessible at the point of care. A recent systematic review and meta-analysis confirmed their value for clinical risk stratification and for targeted exacerbation risk reduction.¹¹⁹ However, more research is needed to define the best way to implement biomarker-driven treatment decisions (see discussion in the section “Is Targeted Treatment Recommended For mild Asthma?”). More effort should be directed toward their implementation at earlier stages of the disease not only at the stage of qualification for biological treatment. Furthermore, these biomarkers are usually measured during

Box 3. Key points for research and clinical practice in mild asthma

1. Although generally considered a benign condition, a proportion of patients with mild asthma can experience severe exacerbations or accelerated lung function decline.
2. Mild asthma should be further coined as “mild asthma syndrome” depicting a heterogeneous population with different pathogenetic pathways, response to treatment, and future risk.
3. Low-dose ICS therapy should be initiated early after asthma diagnosis, whilst patients’ symptoms are mild, to prevent deterioration of their condition. For most patients with mild asthma, symptom control is achievable with low-dose ICS or ICS-formoterol as needed, which are both effective and safe.
4. A small subset of patients with mild asthma might benefit from type 2 biomarker–driven strategies; however, at a population level, this may not be necessary or cost-effective.
5. The goal of achieving biological remission in mild asthma should be emphasized, particularly in patients eligible for AIT.

AIT, Allergen immunotherapy; ICS, Inhaled corticosteroid.

exacerbations or after systemic steroids, which may lead to underestimation of some key drivers of unstable disease.¹²⁰ There is a modest correlation between eosinophil numbers in the airway and those in the blood, but this gets weaker as asthma gets more severe and as patients are exposed to higher doses of corticosteroids.^{121,122} There are still a number of unresolved issues related to the application of blood eosinophil counts in clinical practice, such as the number of measurements demonstrated to be confident in predicting risk and/or the clinical response, or whether blood eosinophils are helpful for both initiating and monitoring the course of therapy. Biomarker measurements must be repeated several times before the exclusion of T2-high asthma. For example, in the UK severe asthma registry, the analysis of historical blood eosinophil counts highlighted a high median (minimum, maximum) value of 350 cells/ μ L (130, 600 cells/ μ L) in the T2-low group, suggesting that most patients had an underlying eosinophilic phenotype.¹²³ Patients with more severe asthma may have persistent sputum eosinophilia with evidence of eosinophilic activity (degranulation and eosinophil peroxidase [EPX] release) but a normal blood eosinophil count.¹²⁴ FeNO appears to be less susceptible to OCS-induced suppression.¹²⁰ Recent health economics evaluations showed that, given its ability to improve the accurate diagnosis of asthma, monitor treatment response, optimize ICS dosing, and identify patient nonadherence, the FeNO testing strategy may improve the management of asthmatic patients leading to significant savings for the national health care systems.¹²⁵⁻¹²⁹ A recent study conducted in the UK primary care system evaluated the barriers and facilitators for the implementation of the FeNO management strategy.¹³⁰ Overall, participants perceived that FeNO-informed asthma management would enhance care if used appropriately and flexibly according to context, for example, planning implementation alongside remote reviews. Easier, equitable access to funded FeNO equipment would be needed for national implementation. Participants suggested that motivation of all involved in future implementation may be increased by guidelines recommending

FeNO and by the use of financial incentives and champions sharing best practice examples.

The secretory activity and turnover of eosinophils, as assessed by measuring eosinophil-derived proteins, may provide an accurate and complementary tool that mirrors the eosinophil activation status.¹³¹ Markers of mast cell activation measured in serum or nasal swabs might also be useful.^{132,133} Other potential T2 biomarkers, such as serum periostin, dipeptidyl peptidase-4, urinary bromotyrosine, monocyte chemoattractant protein-4, and eotaxin-2, lack validated measurement techniques and predicted values.¹³⁴

Nasal secretions and sputum reflect the local inflammatory activity and provide valuable information about the immunological reaction in the lung. Current techniques for nasal secretions sampling are mainly based on 3 principles: collection of spontaneous secretions, nasal washings, and absorption.¹³⁵ Collection of spontaneous secretions is appropriate in subjects with nasal hypersecretion. Nasal washings are associated with unpredictable high dilution, and concentrations of markers often fall below the detection limits of immunological assays. Absorption seems to provide the best compromise between sufficient sample amounts and detectability of inflammatory mediators and IgE. Nasal swabs for eosinophil granule proteins or activation products hold promise.¹³⁶ Using formalin-fixed paraffin-embedded sputum plugs for the easy assessment of sputum eosinophil counts will soon become available at the point of care.¹³⁷⁻¹³⁹ Streamlining the sputum processing to make dispersed fluid an easy biospecimen suitable for rapid assessment tests to identify key markers of inflammation such as EPX, myeloperoxidase, elastase, tryptase, and specific autoantibodies (antinuclear antibodies, anti-EPX, anti-macrophage receptor with collagenous structure, and IgG antibodies) will hopefully also be within reach in asthma centers.¹⁴⁰⁻¹⁴⁸

Lung function can also be considered a biomarker that can be used in guiding therapy. In the Childhood Asthma Management Program cohort, 75% had abnormal patterns for lung growth and early decline: 26% had reduced growth and an early decline, 23% had reduced growth only, and 26% had normal growth and an early decline. Childhood impairment of lung function and male sex were the most significant predictors of abnormal longitudinal patterns of lung-function growth and decline.¹⁴⁹ Small airway dysfunction was associated with a significant exacerbation risk, including in patients with mild asthma, prompting the use of extrafine ICS to decrease the exacerbation rate.⁹¹ BD reversibility was associated with lower risk of severe asthma attacks.¹¹⁹ A study assessing FEV1 decline over 10 years identified older age, higher body mass index (BMI), and increased ICS use as risk factors at 5 years and higher eosinophils, age, ICS dose, and FeNO as risk factors at 10 years. Better baseline lung function was protective both at 5 and 10 years. Thus, all efforts should be directed toward the implementation of lung function testing and lung function trajectories at a larger scale in all facilities managing patients with asthma. Furthermore, BMI emerged as a significant and modifiable marker, underscoring the relevance of monitoring nutritional status in asthma management.

Although currently not point of care, it seems likely that advances in multiomic technology will lead to new bedside tests of mucosal inflammation in asthma in the coming years. Analysis of metabolites in breath (breathomics) might predict sputum eosinophilia, differentiate controlled from uncontrolled

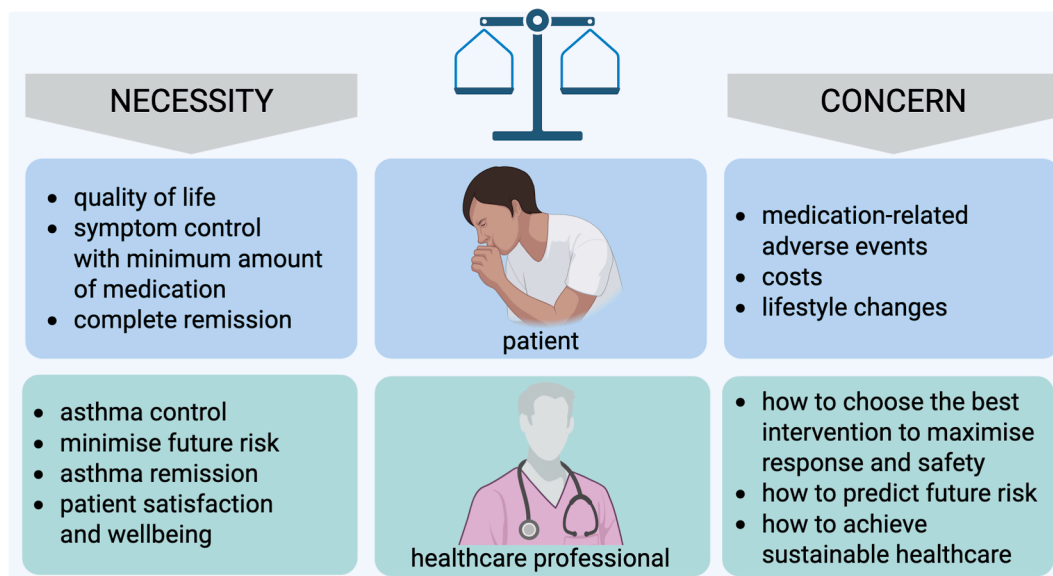


FIGURE 3. The necessity-concern construct in building a personalized asthma management plan. Patients' key beliefs about a management plan determine their common-sense evaluation and thus the extent of adherence. These beliefs primarily consist of 2 categories: the patients' perception of how much they need the specific treatment (quality of life, symptom control, and remission) and concerns about the adverse effects of that treatment, related costs, and lifestyle changes. The health care professional (HCP) supports the patient in achieving balance by delivering tailored education and support. Further, the HCP adds to the construct its own goals (asthma control and remission, risk minimization) and unmet needs (how to tailor the management plan to achieve the best response with less side effects, while being sustainable for the health care system).

asthma, and discriminate steroid-responsive patients from nonsteroid responsive patients.¹⁵⁰⁻¹⁵² "Signatures" observed are not currently quantitative; thus they would be helpful to initiate treatment but not to monitor responses to treatment. In addition, they have not been evaluated to differentiate between various biologic responses. Finally, proteomic and transcriptomic signatures (genes on chips) might become available in a few years.^{153,154} The ultimate goal, as the U-BIOPRED project has envisaged, would be to have a handprint for an individual patient that provides insight into the endotype of that particular patient's asthma, which integrates multiscale omics platforms of imaging, gene, protein, and metabolites.¹⁵⁵ Machine learning algorithms are likely to facilitate integration of these platforms.^{111,156}

Last but not least, it would be very useful to have a noninvasive way to measure airway epithelial barrier dysfunction in asthma, similar to transepidermal water loss measurement of skin barrier in atopic dermatitis. Until then, noninvasive and skin tapes biomarkers can offer significant information on skin barrier dysfunction in asthmatic patients and on lung remodeling.¹¹²

Harmonize recommendations and communication for asthma management at the point of care

Harmonization of asthma management pathways at the point of care is required both at a national and international level (Table I).

The final goal should be a correct diagnosis of asthma and the early identification of future risk, followed by the implementation of a personalized asthma management plan guided by the

asthma theratype. This goal should be clearly communicated to primary care, emergency medicine, other connected specialties, and patients' associations. The messages used should be clear (Table II, Box 4).

IS TARGETED ASTHMA TREATMENT SUSTAINABLE?

In the current funding model, even simple spirometry access is limited, including in the G7 countries. However, our community should continue to educate and advocate for objective measurements that include at the point of care at least lung function testing, FeNO, blood eosinophils, and sputum cell counts. More investigations are needed for patients with severe asthma starting a biological or who exacerbate on biologics.

Point-of-care asthma management based on a stratified approach can be sustainable when integrated into existing workflows, supported by team-based care, and combined with digital tools (eg, electronic health record prompts, mobile applications, connected spirometers, connected inhalers, connected personal monitors, and connected air quality sensors) (Figure 4).¹⁵⁷ Mobile applications and digital therapeutics empower patients to manage their condition and improve adherence to treatments.¹⁵⁸ Telemedicine platforms and remote monitoring devices have the potential to streamline asthma care. It seems likely that AI algorithms will be able to analyze patient data and predict exacerbations in proof-of-concept studies. Although some barriers remain, the return to investment is high, particularly by reducing exacerbations, emergency department visits, and poor asthma control and by improving QoL.

TABLE I. Harmonization of asthma management pathways at the point of care

Action	Tool	Purpose
Symptom control	ACT, ACQ, FeNO, and breathomics	Identify uncontrolled asthma
Lung function testing	Spirometry/impulse oscillometry	Confirm diagnosis and identify small airways disease monitor lung trajectories
Biomarkers	FeNO, blood eosinophils, sputum cytology/mediators/antibodies, and nasal soluble biomarkers	Guide anti-inflammatory strategy
Treatment tuning	Theratype-driven decisions based on visible properties, disease endotypes, and future risk ¹	Improve responder rate
Personalized asthma management plan	Necessity-concern constructs Environmental control Inhaler technique check	Improve adoption by the patient and increase efficacy
Education at every opportunity across the health care continuum	Patient understanding of disease Development of patient skills Changing behavior Learner-centered approach	Support self-management

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FeNO, fractional exhaled nitric oxide.

TABLE II. Messages recommended to be used in the education of health care professionals caring for patients with asthma

“Lung function testing is mandatory for asthma diagnosis”
“Asthma is an umbrella diagnosis so more has to be done to define the disease subtype and guide the choice of treatment”
“Two courses of systemic corticosteroids per year are a red flag and those patients should be referred to a specialist referral center for follow up”
“Longitudinal evaluation and disease trajectories should guide treatment decisions”
“Shared decision making of a personalized asthma management plan is the cornerstone for achieving the best outcomes”

DISCUSSION

The panel identified several gaps and open questions in the implementation of personalized asthma management (Table III).

Asthma remission is emerging as a realistic and achievable goal for selected patients, although it has yet to become a standard target across all asthma severities. Achieving this requires a multifaceted approach that includes multidisciplinary care teams, adaptive management pathways, patient education, and the integration of digital health tools. These elements are critical enablers for sustainable improvements in asthma management at the point of care, ensuring better patient outcomes and optimized resource use.

Despite promising advances in personalized, targeted treatments for asthma, several gaps and challenges remain in their implementation. The expert panel identified key open questions that must be addressed to advance the field (Table III). These include the need for a universally accepted definition of asthma remission in both clinical practice and guidelines, supported by evidence-based recommendations drawn from high-quality RCTs and RWE.

Further research is essential to understand the long-term outcomes of remission-focused strategies, particularly in patients with mild-to-moderate asthma. Identifying reliable biomarkers that predict remission potential remains a priority, requiring innovative trial designs that combine precision immunology with unbiased machine learning approaches.

Box 4. Key points for research and clinical practice for personalized asthma management at the point of care

- (1) An adequate assessment of the individual profile of each patient with asthma and its comorbidities is recommended. This assessment should include disease mechanisms predicting response to treatment, together with disease's future risk.
- (2) Patients and caregivers should engage in shared decision-making and develop adequate management and monitoring plan centered on the balance between necessity (symptom control, quality of life, and disease remission) and concern (side effects and cost of medication, socioeconomic status, lifestyle changes, and environmental control).
- (3) Fractional exhaled nitric oxide and blood eosinophils are the only 2 tests that are currently easily accessible at the point of care. They contribute to risk stratification and for targeted exacerbation risk reduction. More effort should be directed toward their implementation at earlier stages of the disease not only at the stage of qualification for biological treatment.
- (4) More research is needed to define the best way to implement biomarker-driven treatment decisions.
- (5) Harmonization of targeted asthma management pathways at the point of care are required both at a national and international level.

Real-world data on the use of ICS-formoterol and SABA in truly mild asthma cases are still evolving. Determining the role of targeted treatments within specific mild asthma subgroups will depend on improved patient stratification based on underlying disease mechanisms (endotypes) and risk profiles.

In addition, there is an urgent need to reassess the definition of mild asthma in light of emerging ICS-formoterol evidence, supported by more high-quality RWE, including cost-effectiveness analyses. Practical constraints have contributed to the underutilization of stratified medicine tools at the point of care, highlighting the importance of generating stronger evidence for their value and return on investment.

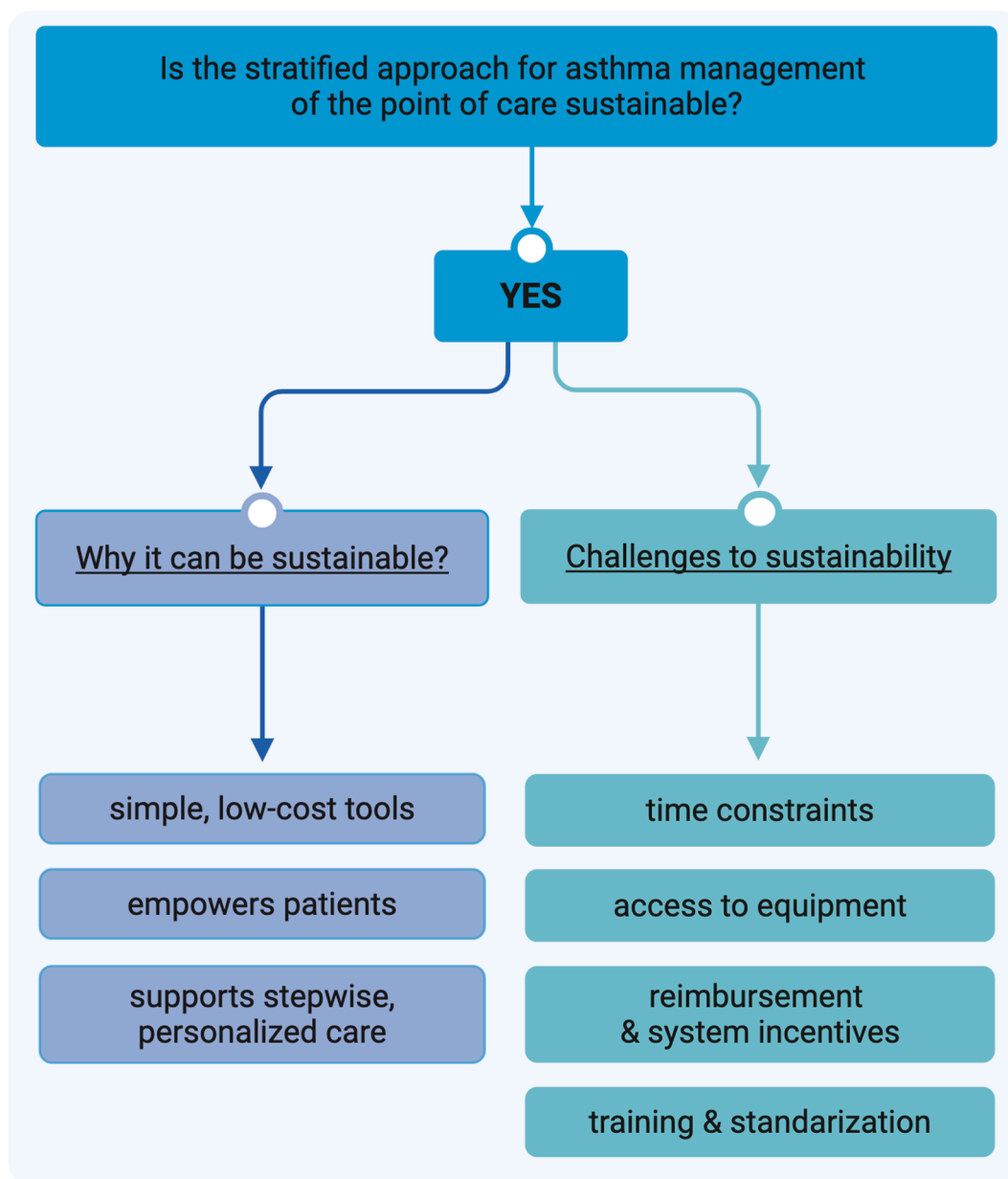


FIGURE 4. Asthma management at point of care using a stratified approach can become sustainable with adequate system support. Simple, low-cost tools focused on detecting the endotype and theratype (blood eosinophils, fractional exhaled nitric oxide, nasal secretions, and sputum) and future risk (risk factors for exacerbations, lung function trajectories, and airway hyper-responsiveness) should be prioritized. Monitoring should use digital tools enabling real-time adjustments to the management plan. Patients should be empowered with the cocreation of a stepwise, personalized care based on the necessity-concern profile. A smart change management approach should tackle the barriers to implementing a stratified approach such as time constraints, access to equipment, reimbursement and system incentives, training, and standardization.

Digital health technologies hold promises for enhancing the sustainability and effectiveness of asthma management, but their impact needs validation through rigorous prospective trials and health economic evaluations. Finally, scaling stratified asthma care in low-resource or high-volume health care settings will require innovative solutions, such as integrating siloed resources into coordinated regional or national networks to optimize cost-efficiency and patient access.

Addressing these challenges through coordinated research efforts and health care innovation will be crucial for realizing the full potential of personalized asthma management and ultimately improving outcomes for patients with asthma worldwide. The global community is closely watching advances in asthma management, as therapies such as dupilumab—first successful in asthma—have now been implemented in COPD and are increasingly being explored for other chronic lung diseases and

TABLE III. Key challenges and research priorities in advancing personalized asthma care

Gaps and open questions	Plans to address	Priority
Lack of common asthma remission definition in guidelines and clinical practice	Evidence-based (GRADE) driven international guidelines based on well-designed prospective RCTs and high-quality RWE	Immediate need
Limited evidence on long-term outcomes of remission-focused strategies in mild-to-moderate asthma	Well-designed prospective RCTs and high-quality RWE (disease registries and prospective effectiveness trials)	Immediate need
What biomarkers best predict remission potential	Adaptive trial design based on biomarkers identified through precision immunology coupled with unbiased machine learning models	Immediate need
Real-world data on ICS-formoterol/SABA use in true mild asthma still evolving	High-quality RWE (disease registries and prospective effectiveness trials)	Immediate need
Is there a role for targeted treatment in specific subgroups of mild asthma	More efforts into stratifying patients with mild asthma based on disease mechanisms (endotype) and future risk of severe exacerbations and/or accelerated lung function decline	Long-term need
Should guidelines redefine mild asthma in light of emerging ICS-formoterol data	More high-quality RWE data on implementation and cost-effectiveness	Immediate need
Underutilization of stratified medicine tools at the point of care due to practical constraints	More evidence for the value proposition based on return for investment models	Immediate need
Can digital health tools improve sustainability and outcomes at point of care	Well-designed prospective RCTs and high-quality RWE (disease registries and prospective effectiveness and health-economics trials)	Immediate need
How can the stratified asthma management at the point of care be scaled in low-resource or high-volume settings	Streamlining siloed resources into regional/national cost-efficient health care networks	Immediate need

GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICS, inhaled corticosteroids; RCT, randomized controlled trial; RWE, real-world evidence; SABA, short-acting β_2 -agonist.

systemic allergic disorders. This cross-disease applicability underscores the broad value of innovation in asthma for shaping the future of precision medicine.

CONCLUSION AND PANEL RECOMMENDATIONS

Stratifying patients according to endotype and risk profile may allow for more tailored therapy and improved outcomes in both mild and moderate-to-severe asthma. Targeted treatment has the potential to become a sustainable asthma care pathway if barriers to stratified care—such as limited resources and cost-effectiveness concerns—are addressed. The panel recommends that the asthma community prioritize the development, validation, and implementation of a stratified approach at the point of care, integrating easily measurable biomarkers with comprehensive clinical judgment to achieve both clinical and biological remission.

Acknowledgments

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