AMERICAN THORACIC SOCIETY DOCUMENTS

Questions in Mild Asthma

An Official American Thoracic Society Research Statement

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Abstract

Background: Patients with mild asthma are believed to represent the majority of patients with asthma. Disease-associated risks such as exacerbations, lung function decline, and death have been understudied in this patient population. There have been no prior efforts from major societies to describe research needs in mild asthma.

Methods: A multidisciplinary, diverse group of 24 international experts reviewed the literature, identified knowledge gaps, and provided research recommendations relating to mild asthma definition, pathophysiology, and management across all age groups. Research needs were also investigated from a patient perspective, generated in conjunction with patients with asthma, caregivers, and stakeholders. Of note, this project is not a systematic review of the evidence and is not a clinical practice guideline.

Results: There are multiple unmet needs in research on mild asthma driven by large knowledge gaps in all areas. Specifically, there is an immediate need for a robust mild asthma definition and an improved understanding of its pathophysiology and management strategies across all age groups. Future research must factor in patient perspectives.

Conclusions: Despite significant advances in severe asthma, there remain innumerable research areas requiring urgent attention in mild asthma. An important first step is to determine a better definition that will accurately reflect the heterogeneity and risks noted in this group. This research statement highlights the topics of research that are of the highest priority. Furthermore, it firmly advocates the need for engagement with patient groups and for more support for research in this field.

Keywords: mild asthma; research needs; definition; pathophysiology; management

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Overview

Mild asthma is believed to represent the majority of patients with asthma. The term has been variably defined but in common usage often refers to patients with infrequent symptoms. These patients can experience an underappreciated exacerbation burden and risk, placing them at increased risk for impaired quality of life (QOL), accelerated lung function decline, and oral corticosteroid exposure with associated adverse events (1–5). There is a lack of concerted research efforts directed toward mild asthma.

In this research statement, a panel of experts evaluated existing literature and made recommendations for future research endeavors. This document is meant to be a roadmap for future research and not a clinical guideline for patient care.

We suggest the following research priorities in various mild asthma–related areas:

A. Definition of mild asthma
   1. Conduct surveys of physician and patient perspectives on how they interpret the term *mild asthma*, whether and why they use this term, how they define it, and what needs to be addressed in the definition of mild asthma.
   2. Conduct a large prospective cohort study of patients with "well-controlled" asthma (without defining mild asthma *a priori*) to better understand and define features of mild asthma.
   3. Develop a consensus definition of mild asthma that will have utility for patients, clinicians, and researchers.

B. Mild asthma phenotypes and inflammatory mechanisms
   1. Investigate inflammatory pathways in mild asthma using airway samples with multiomics (e.g., breathomics) and network analyses.
   2. Conduct cluster analyses of mild asthma populations to better elucidate heterogeneity in this group.
   3. Describe mild asthma phenotypes using a multidimensional approach that includes airway hyperresponsiveness (AHR), exacerbation patterns, symptom burden, and inflammation.
   4. Assess whether there is a treatment-refractory or poorly corticosteroid responsive phenotype in mild asthma.
   5. Conduct large epidemiological studies to better understand the stability and predictive value of blood eosinophils in mild asthma and to improve our understanding of the implications of variable eosinophil counts.
   6. Conduct large epidemiological studies to understand the stability and predictive value of breath analysis in mild asthma.
   7. Characterize the stability of inflammatory markers/phenotypes in the setting of various environmental triggers (viral infections, allergen exposure, air pollution, weather change, stress) and mechanisms for recovery from them.

C. Mild asthma disease progression and exacerbations
   1. Investigate mild asthma phenotypes regarding the risk of progression, response to treatment, and the influence of various triggers.
   2. Conduct prospective longitudinal cohort studies to identify the frequency of/risk factors (clinical and inflammatory characteristics) for the progression of mild asthma to more severe disease.
   3. Monitor long-term outcomes of patients with mild asthma followed exclusively by primary care providers (e.g., patients with only seasonal symptoms).
   4. Conduct longitudinal studies evaluating the influence of various exacerbation severities on progression from mild asthma to more severe asthma.
   5. Evaluate patient factors influencing the exacerbation reduction effects of mild asthma therapies.

D. Mild asthma treatments
   1. Identify patients who need daily inhaled corticosteroid (ICS)–containing treatment, rather than ICS used whenever an as-needed reliever is taken.
   2. Determine if ICS-containing treatment is required in all populations with mild asthma.
   3. Identify populations that will benefit most from ICS therapy in terms of exacerbation reduction and symptom control.
   4. Conduct real-world and long-term follow-up studies evaluating the efficacy and safety of as-needed ICS plus rapid-acting bronchodilator regimens.
   5. Evaluate the benefits of ICS therapy in patients with elevated fractional exhaled nitric oxide (F_{ENO}) concentrations but otherwise controlled mild asthma.
   6. Identify whether treatment strategies should differ between adolescents and adults.
   7. Identify predictors of treatment response in mild asthma and whether the predictive value of type 2 (T2) biomarkers varies depending on the criteria chosen to define ICS response.
   8. Evaluate the safety and efficacy of as-needed ICS plus a short-acting β-2 agonist (SABA) compared with a SABA alone, versus as-needed ICS–formoterol, versus maintenance ICS plus as-needed SABA in patients with newly diagnosed asthma and patients with mild asthma.
   9. Investigate fluticasone furoate plus long-acting β-2 agonist (which has a prolonged duration of antiinflammatory effect) for twice-weekly use as a step-down option compared with continuing daily treatment.
   10. Assess the efficacy and safety of stepwise algorithms across the range of asthma severity, including mild asthma.
   11. Investigate how beliefs and behaviors about SABA-only treatment (among patients, clinicians, and policy makers) can be changed and how to communicate the importance of population-level risk reduction strategies when symptoms are infrequent.
   12. Explore the effect of biologics in well-characterized patients with mild asthma to identify those who may benefit from early introduction of therapy (e.g., by identifying biomarkers for relative corticosteroid refractoriness).
   13. Standardize outcomes for studies of allergen immunotherapy (AIT) using validated scales and exacerbations as end points.
   14. Characterize the patients with mild asthma who respond best to AIT.
   15. Conduct head-to-head comparative studies to assess the size of effect of AIT compared with other therapies.

E. Nonpharmacological interventions (NPIs) in mild asthma
   1. Evaluate the efficacy of aerobic exercise programs in mild asthma.
   2. Assess long-term outcomes of different breathing exercises in patients with mild asthma, particularly in those with suspected dysfunctional breathing.
   3. Evaluate the short-term and long-term benefits of diet and antioxidant foods in obese and nonobese patients.
   4. Evaluate the benefit of weight loss in obese patients with mild asthma and whether benefit varies by age group.
   5. Evaluate cognitive behavior therapy (CBT) and pharmacotherapy in patients with mild asthma and concomitant anxiety and/or depression.
   6. Evaluate the benefits of therapeutic patient education (including a written action plan) in mild asthma.

F. Pediatric research needs in mild asthma
   1. Determine the best definition of mild asthma in the pediatric population.
   2. Determine the best approaches for the early detection of children at risk of progression from mild to more severe asthma and whether interventions can alter this progression.
   3. Evaluate whether personalized treatment strategies based on a phenotype or an endotype approach lead to improved treatment response.
   4. Evaluate the efficacy and safety of as-needed ICS, either alone or in combination with SABA or formoterol, in children with mild asthma.
   5. Evaluate the long-term consequences in terms of exacerbation risk and lung growth with intermittent or as-needed ICS plus rapid-acting bronchodilator use compared with daily ICS plus a bronchodilator.
   6. Evaluate the impact of patient-oriented and health services research on positive change in home and community environmental conditions and its effectiveness to improve asthma outcomes in pediatric asthma.
   7. Evaluate the impact of patient-oriented and health services on positive change in home and community environmental conditions and its efficacy to improve asthma outcomes in pediatric asthma.

G. Patient perspective on research on mild asthma
   1. Evaluate patient education that specifically targets patients with mild asthma.
   2. Define symptom severity and frequency in a way that helps patients recognize and treat their asthma optimally.
   3. Investigate medication adherence strategies in mild asthma that can help patients who are prescribed daily treatment be motivated to maintain their antiinflammatory treatment.
   4. Investigate whether NPIs can help reduce medication requirements in patients with mild asthma (such as anxiety and monitoring [e.g., peak flow]).

Introduction

Asthma affects approximately 339 million individuals worldwide (6) and 24 million individuals in the United States (7). Although most asthma research efforts have focused on severe asthma (8), patients with mild asthma constitute the majority of people with asthma (50–75%) (9) and have been relatively overlooked and understudied (10). The term *mild asthma* has various definitions (Table 1), but it is often used to refer to patients with infrequent or easily relieved symptoms. However, patients with mild asthma can experience an underappreciated exacerbation burden, which places them at increased risk for accelerated lung function decline and oral corticosteroid exposure with associated adverse events (1–5). Furthermore, 30–37% of acute asthma episodes, 16% of near-fatal asthma episodes, and 15–27% of fatal attacks occurred in patients reporting symptoms less than weekly or only with exertion in the preceding 3 months (9, 11). Finally, many patients with mild asthma are managed solely with SABAs, which provide only symptom relief, without treating the underlying airway inflammation that is contributing to symptom burden and exacerbation risk (12–14). Therefore, mild asthma is not a benign disease for many patients, and the recent Global Initiative for Asthma (GINA) (15) update advocates reconsideration of its definition to more fully encompass associated risks and allow better communication with patients. The current American Thoracic Society (ATS) classification of asthma severity is based on the degree of treatment needed to control asthma (16, 17), which often excludes consideration of exacerbation frequency.

Challenges surrounding research on mild asthma include the variability of existing definitions, heterogeneity of both clinical features and inflammatory markers, the focus on severe asthma research that overlooks the needs of most patients with asthma, and the absence of unified patient advocacy for research on mild asthma (Figure 1). Interest in mild asthma has intensified (*see* Table E1 in the online supplement) after the recent publication of large clinical trial results that led to significant changes in the GINA strategy (10, 15). Given the complexity surrounding research on mild asthma, leaders in the field identified a need to acknowledge current knowledge gaps and make recommendations for future research.

This document summarizes these gaps and recommendations in the form of a research statement intended to inform and guide research priorities in mild asthma. It is not intended to be used as a clinical practice guideline.

Methods

See the online supplement for further details.

Committee Composition

Our diverse expert panel consisted of 24 members, including 4 co-chairs (K.S., N.A.H., N.L.L., and A.M.) (*see* Tables E2 and E3). Experts were divided into three groups; co-chairs were assigned to oversee each group, and topics were assigned for presentation at three virtual meetings. One group was composed of patients, caregivers, and stakeholders (including from the American Lung Association Patient Advisory Group) to obtain their perspectives on research needs.

Table 1. Common Definitions Used for Mild Asthma

		On Controller Treatment?	Mild Asthma Definition	
Clinical definitions	NAEPP 2007 (18)	No	*Intermittent* Symptoms: ⩽2 d/wk Nighttime awakenings: ⩽2 times/month SABA use: ⩽2 d/wk Interference with normal activity: none $FEV_1 > 80\%$ predicted, FEV_1/FVC ratio greater than normal Exacerbations: 0 or 1/yr	*Persistent* Symptoms: >2 d/wk but not daily Nighttime awakenings: 3 or 4 times/mo SABA use: >2 d/wk but not daily Interference with normal activity: minor $FEV_1 > 80\%$ predicted, FEV_1/FVC ratio greater than normal Exacerbations: ⩽2/yr
	2009 ATS/ERS task force (17)	Yes	After exclusion of modifiable factors such as poor adherence, smoking, and comorbidity, mild asthma is "easy to treat" (i.e., asthma control is achieved with low intensity of treatment).	
	GINA 2022 (10)	Yes	*Mild asthma* is defined as asthma that is well controlled with as-needed ICS–formoterol alone or low-dose ICS. GINA does not distinguish between intermittent and mild persistent asthma.	
Research definitions (examples)*	Based on symptoms	?	Symptoms: at least weekly, not daily in the last 3–6 mo (e.g., Busse *et al.* [88] and Papi *et al.* [90])	
	Based on treatment	Yes	GINA step 1 or 2 therapy for 1 mo (e.g., O'Byrne *et al.* [21])	
	Based on lung function	?	Prebronchodilator $FEV_1 \leqslant 75\%$ predicted (e.g., Papi *et al.* [90])	

Definition of abbreviations: ATS = American Thoracic Society; ERS = European Respiratory Society; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; NAEPP = National Asthma Education and Prevention Program; SABA = short-acting β_2 agonist.
*Usually, two or more criteria are combined.

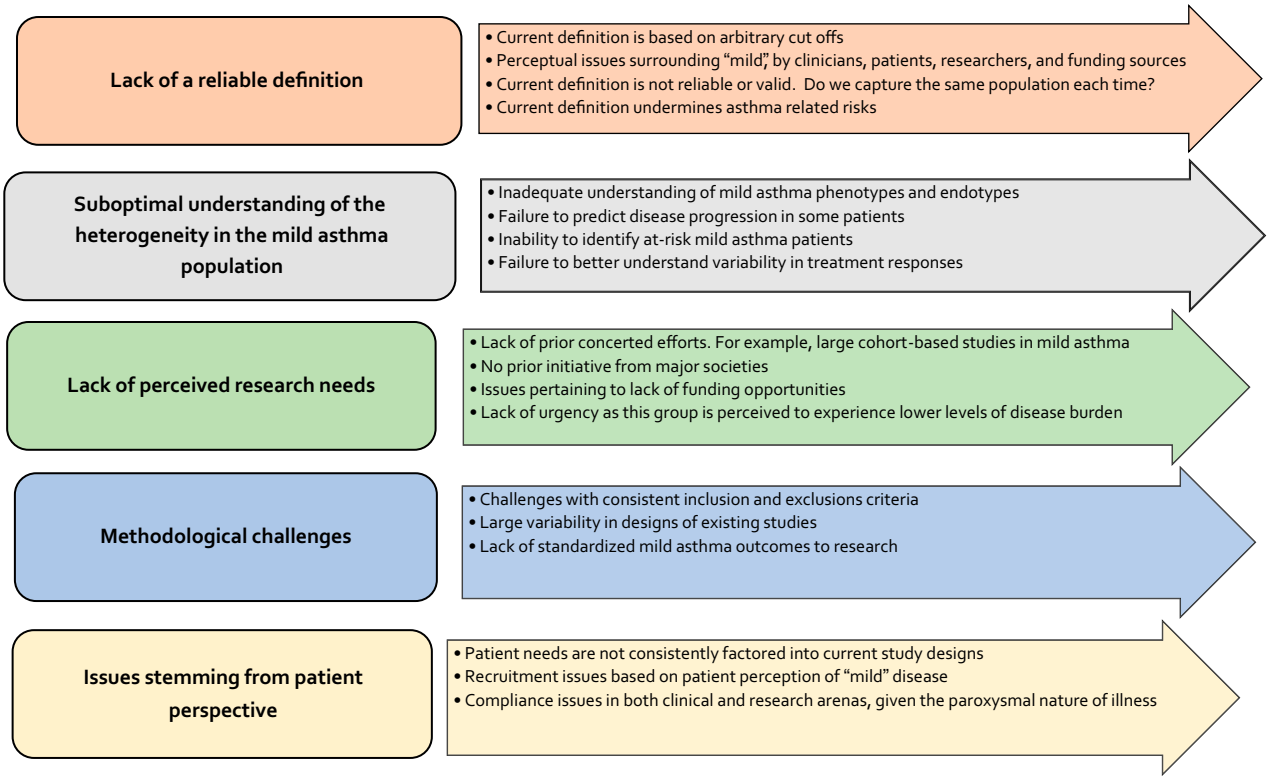

Figure 1. Current challenges in research on mild asthma.

Literature Search and Evidence Appraisal

Three overarching topics were discussed in virtual meetings: *1*) pathophysiology, *2*) management, and *3*) patient perspectives. The co-chairs requested a literature review and presentation from preidentified panel speakers (*see* Table E4).

Research Recommendations

Each group summarized the existing evidence and identified gaps. Recommendations were formulated by discussion and consensus. Research gaps presented in this document were considered the most important questions for mild asthma.

Document Development

Speakers summarized their presentations and literature reviews in a written document. The sections were reviewed, collated, and circulated by the co-chairs. The expert panel members were then asked to volunteer for writing committees (*see* Table E5). Writing committee members were provided with synthesized summary drafts, and feedback was collected. Once edits were made, a combined document was circulated among the entire panel for review and comments.

Definition of Mild Asthma

Current Knowledge and Challenges

The lack of a standardized definition of mild asthma has been a major challenge for clinical research (Table 1 and Figure 1). In the current ATS definition, published in 2008 and 2009 by an ATS/European Respiratory Society (ERS) task force (16, 17), asthma severity is defined by difficulty in controlling asthma with treatment; mild asthma is considered as asthma that can be controlled with low-intensity treatment. The task force included both symptoms and exacerbations in the assessment of control but recognized that exacerbations could be experienced even by patients with mild asthma. It emphasized that severity could be assessed only once patients had been taking controller treatment for several months, as uncontrolled asthma before starting treatment could turn out to be mild, moderate, or severe depending on the response to ICS (16).

GINA, following the ATS/ERS definition, defines mild asthma as asthma that is well controlled on steps 1 and 2 of treatment (with both steps containing ICS). However, the 2020 focused update of the National Asthma Education and Prevention Program (NAEPP) guidelines (18) retains the NAEPP 2007 (19) division of mild asthma before controller treatment is started (i.e., in treatment-naive patients or in patients receiving SABAs alone), into "intermittent" versus "persistent" on the basis of daytime symptoms, nighttime awakenings, interference with daily activity, and exacerbations in the setting of normal lung function. Before controller treatment is started, GINA (unlike NAEPP) does not distinguish between intermittent and persistent asthma because, as noted above, severity can be assessed only after the patient is on controller treatment, because of a lack of evidence to support specific symptom frequency criteria, and because both groups experience similarly large reductions in exacerbations with ICS treatment (10, 20). After controller treatment is started, NAEPP continues to distinguish between intermittent and persistent asthma:

intermittent if it can be controlled by SABA-only treatment and persistent if step 2 treatment or higher is required.

There are significant limitations to the utility of the ATS/ERS definition of mild asthma for both clinical practice and clinical trials, as highlighted in GINA 2022 (10). This definition was intended as a retrospective label for clinical practice, but few patients in clinical practice have had their controller treatment stepped down to assess the minimum step at which their asthma remains controlled. It is not suitable for assessing clinical trial eligibility because of the time needed to establish the minimum effective treatment and the sporadic nature of exacerbations and because many clinical trials require asthma to be uncontrolled at entry. The exception is step-down studies; for example, 55% of the SYGMA (Symbicort Given as Needed in Mild Asthma) populations (21, 22) included patients considered by their physicians to have controlled asthma on ICS or leukotriene receptor antagonists (LTRA).

In addition, our review revealed that the patient populations included in previous studies of mild asthma have been heterogeneous and rarely consistent with the above definitions. Inclusion criteria for clinical trials have typically been based on symptom frequency (sometimes with an upper frequency limit), treatment degree, minimum values of FEV_1, or a combination of these factors (23). Many studies also require patients to have some impairment of FEV_1 and significant bronchodilator responsiveness at entry (to confirm the diagnosis of asthma), but these are also typical features of uncontrolled asthma.

A standardized definition of mild asthma for clinical research could decrease heterogeneity among studies, thereby making comparisons of study results more generalizable. However, the undertaking of defining it is fraught with challenges (24). Specific challenges include the following

1. An inherent difficulty is that asthma severity by its own definition/nature varies over time. This makes it impossible to select a cutoff point to define categorical severity groups during cross-sectional assessments.
2. In addition to variable disease activity, definitions underappreciate the heterogeneity in this population, such as not including patients with infrequent (rare but significant) events.
3. Moreover, there is a risk of failing to identify patients who may be at higher risk of poorer outcomes or disease progression and would thus require more aggressive management approaches (9).
4. It is essential that a standardized definition have utility for the fields in which it will be used (e.g., clinical practice, clinical trials).

Future research on mild asthma, suggested in this document, will provide the tools instrumental to circumventing these challenges, bridging knowledge gaps, and hence developing a widely accepted definition. In the interim, this *ad hoc* committee proposes the following working definition of mild asthma.

Working Definition of Mild Asthma

To address this complex issue, a subgroup of experts (A.M., N.L.L., K.S., P.M.B., A.P., D.P., R.B., H.K.R., and N.A.H.) was convened to determine the best approach to leverage the panel's expertise in this area. A REDCap survey (Vanderbilt University) developed by the subgroup was administered to the expert panel. The full survey as well as the responses from the 22 experts who completed the survey are included in Table E6.

Although there were common features, there was significant heterogeneity in responses. However, we propose the following definition: **Mild asthma is asthma that is characterized by minimal symptoms and risk in patients *on SABA alone, as-needed ICS with SABA, as-needed ICS–formoterol, or daily ICS plus SABA or those who are not on any therapy***. On the basis of the survey results, our expert panel members suggested the following parameters for defining impairment and risk in patients with confirmed diagnoses on such treatment:

- *Daytime symptoms fewer than two per week (impairment domain)*
- *Nighttime symptoms fewer than one per month (impairment domain) (but many members believed that any night waking represented poor control)*
- *Fewer than one exacerbation per year (risk domain) (but many members strongly believed any exacerbations during the year to represent more severe illness)*
- *Preserved lung function (e.g., postbronchodilator FEV_1 greater than the lower limit of normal) (risk domain)*

Strengths of the Working Definition

The obvious merit of our working definition is that it integrates impairment with risk, alluding to more longitudinal assessments of patients, as opposed to cross-sectional assessments of control in some of the existing definitions. The intent of proposing this working definition is to provide a starting point for future research in this space.

The panel emphasized that it is imperative to first confirm the asthma diagnosis. Diagnostic challenges (25) noted in the general asthma population most certainly pertain to mild asthma as well, and the role of available tests needs to be reevaluated carefully, as is being done in parallel efforts (26).

As intended, our working definition captures patients with the mildest manifestations of disease and addresses needs in both the clinical and research arenas. Our definition also clearly focused on the influence of treatment on severity classification. In the survey, when participants were asked if the symptom and exacerbation thresholds needed to be met only while patients were *off* treatment, 36% disagreed, and 50% conceded that this would be impossible to implement, as it would require patients and family members to recall remote asthma history, and asthma severity can change over time. Thus, an elevated risk of recall bias makes this infeasible. Hence, although not unanimous but based on a clear majority of opinion, our definition included severity assessment on specific low-intensity asthma therapies or patients with low impairment plus low risk while off any treatment.

Shortcomings of the Working Definition

As evident in the above discussion, the parameters of this definition were not unanimously supported by the expert respondents but represent the majority view.

This reflects the limitations of available mild asthma understanding and research rather than a shortcoming of this project. For example, research is yet to ascertain whether a single exacerbation per year has an impact on the natural progression of mild asthma. Hence, the greatest variation noted related to the criterion for exacerbations. Although some respondents (8 of 22) favored zero exacerbations in the previous year, others believed that having an exacerbation (triggered by a viral illness, for example) in patients with otherwise low impairment or risk does not exclude their being classified as having mild asthma. An alternative approach in the future could be to assess exacerbation frequency longitudinally and define mild asthma as asthma with fewer than one exacerbation per year on average (e.g., one exacerbation every 2–3 yr). Other potential complexities with defining mild asthma identified from the survey include the variability of disease activity and in the intensity and duration of symptoms and the challenges of accommodating the two components of control: impairment and risk. It is not known whether outcomes differ between patients with concordant (e.g., poor symptom control and one exacerbation per year) and discordant (e.g., one exacerbation per year but few symptoms or frequent symptoms without exacerbations) features. Last, there was no consensus on whether the specific study design should be taken into consideration when defining the population, specifically whether criteria could be adjusted for specific research designs (e.g., observational, interventional, mechanistic).

We were also unable to apply our definition in our current literature search, as it would have excluded a majority of studies currently referred to for the treatment of mild asthma. In summary, our definition is limited by research gaps in mild asthma, specifically in the areas of heterogeneity (clinical and inflammatory) and risk assessment.

Proposed Research to Define Mild Asthma

More work on the definition of mild asthma is needed. It is important to further survey physicians, patients, and caregivers on their current interpretations of this condition and its burden. Shaping a definition with such a survey can meaningfully influence its widespread and provide valuable insights. Prior such efforts have guided treatment preference in mild asthma, for example (27). Another approach may be to prospectively study cohorts of patients with well-controlled asthma and then capture features that would be acceptable to clinicians and/or patients themselves to be classified as having mild asthma (Table 2). We would also support research that evaluates the longitudinal trajectory of patients with mild asthma from historical data sets to weigh the influence of each criterion on impairment or risk.

Finally, although speculative, alongside building alternative approaches to existing efforts, there may be value in moving away from a "mild, moderate, or severe" classification and instead focusing on "controlled versus not controlled" and "low risk versus high risk" of exacerbation, loss of lung function, or future poor control.

Table 2. Research Needs for the Definition of Mild Asthma

Knowledge Gaps
Mild asthma definitions currently used in clinical practice and research
Current interpretation of the term *mild asthma* by patients, clinicians, and the general community and its implications for health and treatment needs
Research outcomes that should be addressed in a future definition of mild asthma
Suggested Research
Conduct surveys of physician and patient perspectives on how they interpret the term *mild asthma*, whether and why they use this term, how they define it, and what needs to be addressed in the definition of mild asthma
Conduct a large, prospective cohort study of patients with "well-controlled" asthma (without defining mild asthma *a priori*) to better understand and define features of mild asthma
Develop a consensus definition of mild asthma that will have utility for patients, clinicians, and researchers

However, at this nascent stage, we should be cautious not to overvalue risk or control-based reclassification. It is challenging, for example, to take the heterogeneous "mild asthma syndrome" and divide it categorically on the basis of risk or control. Furthermore, as impairment and risk can be discordant, this classification schema must be multidimensional.

Pathophysiology of Mild Asthma

Mild Asthma Phenotypes and Inflammatory Mechanisms

The phenotypic description of mild asthma should be considered in several dimensions: airway responsiveness, pathophysiology, inflammatory phenotype, exacerbation pattern, and longitudinal clinical symptom burden.

Mild asthma demonstrates heterogeneity in inflammation that likely emanates from specific and nonspecific triggers at the airway epithelium, potentially interacting with different underlying genomic patterns, and that may also be influenced by current exposures, such as to allergen. Although the frequency of particular phenotypes may differ in mild compared with moderate to severe asthma, there is still a spectrum of inflammatory disease present in mild asthma. This is highlighted by *post hoc* analysis of patients with mild asthma in the SARP (Severe Asthma Research Program) I/II (defined by having $FEV_1 \leqslant 80\%$ predicted on no or low doses of ICSs). The mild asthma cohort was more likely to have early-onset asthma (age <12 yr), was predominantly female, and exhibited some atopy (28). These patients with mild allergic asthma were on no or low- to moderate-dose ICS and had low healthcare resource use. In SARP III, 40% of patients with early-onset asthma had elevated blood eosinophils, 20% had elevated sputum eosinophils, and 60% had elevated sputum neutrophils (highest cell count noted on repeat measures) (29). Comparable results were noted in baseline assessments for the SIENA (Steroids in Eosinophil Negative Asthma) study in which only ~25% of patients had elevated sputum eosinophils (30). As in the SARP studies, patients with mild asthma in SIENA tended to have early-onset disease, needed fewer controllers, were usually atopic, had more preserved lung function, and had lower healthcare use.

Inflammatory mechanisms in asthma include upregulation of allergic, eosinophilic, mixed allergic/eosinophilic, and neutrophilic pathways. The triggers that modulate allergic inflammation are related to underlying sensitization that results in T-cell differentiation and production of IL-4–mediated B-cell isotype switching to IgE-producing B cells. IgE is critical in early and late allergic responses that result in mast cell degranulation. Stimulation of alarmin production can result in the upregulation of type 2 innate lymphoid cell production and the increased production of IL-5 by T cells, with resultant eosinophilic inflammation. Nonallergic triggers such as viruses and tobacco smoke can result in the upregulation of IL-17, which results in neutrophilic inflammation (31). It is notable that even those with "mild intermittent" asthma can have underlying airway inflammation (32, 33), indicating that even in the mildest clinical presentation, inflammation is still a hallmark of disease. Airway inflammation and remodeling have also been demonstrated in asymptomatic subjects with AHR, a condition that sometimes precedes symptomatic asthma (34). Inflammatory pathways in mild asthma are as heterogeneous as in severe asthma (35). Cluster analyses have furthered our understanding of inflammation in mild asthma with the identification of both a cluster of eosinophilic patients in SARP and a cluster with minimal airway inflammation in both the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) and ADEPT (Airway Disease Endotyping for Personalized Therapeutics) cohorts (28, 36, 37). Interestingly, the application of an eosinophilic phenotype prediction scale revealed a high prevalence of eosinophilic phenotypes in both a primary care cohort (38) and a large severe asthma registry (39). In the former, 72.5% of the patients were most likely or likely to have an eosinophilic phenotype on the basis of both clinical features and biomarkers. The prevalence of a noneosinophilic phenotype was low (5.6%) (38). In contrast, 47% of patients with mild to moderate asthma in an Asthma Clinical Research Network cohort showed no evidence of persistent eosinophilic disease (40). These disparate findings suggest that although eosinophilic inflammation is common in mild asthma, this may differ on the basis of clinical characteristics, comorbid disease, and inhaled therapy treatment intensity; differences among populations or countries may also depend on differing environmental factors, such as air pollution and exposure to allergens or endotoxins. It is well accepted that severe asthma is associated with upregulation of multiple inflammatory pathways with both type 1 and type 17 cell activation in addition to T2 responses. However, airway inflammation in mild asthma is more likely to be T2 (41), and the importance of non-T2 inflammation in mild asthma is an area of ongoing investigation.

Interpretation of these phenotypes and mechanisms must also take background medications into account, as ICS may suppress T2 inflammation and can lead to an overestimation of non-T2 phenotypes, although this group is still a minority in most studies of mild asthma. Inflammatory phenotype may vary over time, with eosinophilic inflammation increasing after allergen exposure (42–44) or during exacerbations (43–51) and decreasing with ICS therapy (52). Even low-dose ICS attenuates the early and late asthmatic responses and reduces eosinophilic response in mild allergic asthma (53). A similar degree of airway inflammation and subepithelial fibrosis is noted in recent ($\leqslant$2 yr) versus long-standing ($\leqslant$13 yr) mild asthma, and high-dose ICS therapy results in improvements in AHR after 8 weeks of therapy in both cases (54). Furthermore, normalization of airway eosinophilia and significantly decreased AHR is possible with long-term ICS therapy in some but not all patients (55). Last, it is important to note that smoking in mild asthma may modify the effects of ICS on airway inflammation (Table 3) (56, 57).

Table 3. Research Needs for Mild Asthma Phenotypes and Inflammatory Mechanisms

Knowledge Gaps
Clinical outcomes of different mild asthma phenotypes including specific populations (mild asthma in elderly, obese, athletes, etc.)
Mild asthma phenotypes and their stability (e.g., whether they change with allergen exposure, pollution, exacerbation frequency, and over time)
Which phenotypes of mild asthma are at greater risk (e.g., of severe exacerbations)
Role of eosinophils in mild asthma regarding pathobiology, associated risks, and outcomes
Other inflammatory pathways of mild asthma and whether/how they differ from those in more severe disease
Optimal study designs for research into mild asthma pathobiology
Suggested Research
Investigate inflammatory pathways in mild asthma using airway samples with multiomics (e.g., breathomics) and network analyses
Conduct cluster analyses of mild asthma populations to better elucidate heterogeneity in this group
Describe mild asthma phenotypes using a multidimensional approach that includes AHR, exacerbation patterns, symptom burden, and inflammation
Assess whether there is a treatment-refractory or poorly CS responsive phenotype in mild asthma
Conduct large epidemiological studies to better understand the stability and predictive value of blood eosinophils in mild asthma and to improve our understanding of the implications of variable eosinophil counts
Conduct large epidemiological studies to understand the stability and predictive value of breath analysis in mild asthma
Characterize the stability of inflammatory markers/phenotypes in the setting of various environmental triggers (viral infections, allergen exposure, air pollution, weather change, stress) and mechanisms for recovery from them

Definition of abbreviation: CS = corticosteroid.

Disease Progression and Exacerbations

Mild asthma progression is associated with epithelial injury, inflammation, and airway remodeling and may correlate with AHR (58–61). Compared with the general population, patients with self-identified asthma have larger declines in FEV_1 over time (62). These effects can be attenuated partially with treatment (53–55). Some patients with mild asthma (~3–20%) evolve to severe asthma, although it is unknown ow to predict those with a risk of poorer outcomes, and it remains possible that the initial clinical assessment of asthma severity was incorrect (63, 64). Clinical factors associated with progression and an increased risk of developing severe asthma include inappropriate SABA use, older age at onset, and the presence of comorbidities (59). Interestingly, mild, early-onset asthma that is atopic or eosinophilic does not generally appear to worsen over time, despite long-term repeated exposure to allergic triggers, at least in the research environment (65). Finally, although it has been postulated that some subpopulations of mild asthma may experience steeper declines in lung function on the basis of their inflammatory phenotype (66), this remains relatively unexplored.

The observation that even patients with mild asthma experience exacerbations (0.12–0.77 per patient-year) reinforces the importance of exacerbations in this population (67, 68). In clinical trials, rates of severe exacerbations in patients with mild asthma range from 0.20 to 2.88 per year (23). Exacerbations can be associated with lung function decline, especially in younger adults (69). Severe exacerbations in patients not randomized to ICS in the START (Steroid Treatment as Regular Treatment in Early Asthma) study were noted to be at risk for accelerated FEV_1 decline (70). Similar effects were noted in patients with more than two exacerbations per year in a cohort of 108,182 patients (71). 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.

The question remains: how do we prospectively identify characteristics of patients with mild asthma who experience adverse outcomes from exacerbations (e.g., exacerbations that lead to future lung function decline)? A recent observational study of 773 patients, one-third on GINA steps 1 and 2 therapy, demonstrated that physiological tests (including impulse oscillometry) of small airway disease are also predictors of important asthma outcomes, including control and exacerbation (72). Although unclear, other biomarkers or T2-associated comorbidities (e.g., F_{ENO}, eosinophils, nasal polyposis) similarly hold the potential for being predictors (73, 74). It is also uncertain to what extent exacerbations weigh in the evaluation of mild asthma, as the prescriber's threshold to prescribe an oral corticosteroid or patient expectations to receive this therapy will influence the reporting of "exacerbations." In this paradox, the treatment determines the identification of the event rather than, as in most clinical contexts, the event determines the treatment. Hence, research on mild asthma also requires a reproducible definition of exacerbations. It is notable that although exacerbations may occur in patients with mild asthma, there are some subpopulations of patients that appear to bear the burden of asthma-related morbidity and mortality. Within the ultrasound, Black and Puerto Rican children and adults have significantly higher exacerbation frequency and emergency department visits (75, 76). It is unlikely that observed disparities result purely from biologic differences in populations (such as airway inflammation or differential responses to treatment) (77–79). These disparities in asthma outcomes are likely due to socioeconomic and environmental exposures (such as nutrition, exposure to violence, pollution, stress, and education) (80–84) as well as differential treatment paradigms in these populations, and this warrants further assessment (85, 86). Globally, 96% of asthma deaths occur in low- and middle-income countries, and many populations lack access to even the most basic inhaled asthma medications (87). We must focus on strategies that improve the implementation of appropriate treatment approaches in all patients with asthma and close the gaps in our understanding of implementation gaps that differentially affect certain groups (Table 4).

Table 4. Research Needs for Understanding Mild Asthma Disease Progression and Exacerbations

Knowledge Gaps
Progression of mild asthma to more severe clinical expressions: common vs. rare evolution? Factors that are associated with the progression of mild asthma to moderate and severe asthma (lung function decline, frequent exacerbations, etc.)
Definition and characterization of exacerbations in mild asthma
Mechanisms to identify patients with mild asthma at risk for exacerbations
Which subpopulations of mild asthma are at higher risk of poorer outcomes
Better understanding of the influence of external triggers (respiratory viruses, allergens, etc.) on mild asthma exacerbations
Mild asthma disease progression in patients with seasonal asthma and those followed exclusively by primary care providers
Suggested Research
Investigate mild asthma phenotypes regarding the risk of progression, response to treatment, and the influence of various triggers
Conduct prospective longitudinal cohort studies to identify the frequency of/risk factors (clinical and inflammatory characteristics) for the progression of mild asthma to more severe disease
Monitor long-term outcomes of patients with mild asthma followed exclusively by primary care providers (e.g., patients with only seasonal symptoms)
Conduct longitudinal studies evaluating the influence of various exacerbation severities on progression from mild asthma to more severe asthma
Evaluate patient factors influencing the exacerbation reduction effects of mild asthma therapies

Management of Mild Asthma

Treatments Currently Available in Many Countries for Mild Asthma

Regular (daily) use of ICS. The START study revalidated that in mild asthma, low-dose ICS taken regularly with a SABA reliever reduced exacerbation risk and symptom burden and improved lung function compared with a SABA alone (88). However, ICS did not reduce the rate of lung function decline over time, except for subjects experiencing severe exacerbations (89). The greater efficacy of regular ICS plus SABA over a SABA alone has also been confirmed in the BEST (Beclomethasone plus Salbutamol Treatment), SYGMA 1, and Novel START studies (21, 90, 91). The efficacy of regular low-dose ICS over SABA in Novel START for reduction of exacerbations increased with baseline blood eosinophils (92).

In a prespecified subgroup analysis of biomarkers from SIENA (93), sputum eosinophils, blood eosinophils, and F_{ENO} predicted ICS response by the composite outcome. A similar proportion of adult participants in both the SIENA and Novel START studies had blood eosinophils $<$150 cells/μl and $>$300 cells/μl, and the response to (benefit from) ICS was associated with a higher blood eosinophil count ($\leqslant$300 cells/μl) in both studies. The other potential predictive biomarker in adults is F_{ENO} (94), with a F_{ENO} $\leqslant$15 ppb in patients with low sputum eosinophils not on ICS, potentially identifying adults who will benefit from ICS (30). In SIENA, none of the T2 biomarkers was predictive of ICS response in adolescents; only the number of positive aeroallergens and IgE concentrations were predictive.

Subgroup analyses conducted in patients reported to have intermittent asthma indicated a superiority of regular low-dose ICS plus a SABA reliever inhaler over a SABA alone for reduction of exacerbations was also seen in this group (20, 95). Finally, although the addition of long-acting β-2 agonists (LABAs) to low-dose ICS was not better than regular ICS in preventing exacerbations in patients with mild asthma (96), once-daily low-dose ICS/LABA has been successfully tested as an effective step-down strategy from twice-daily low-dose ICS in the LOCSS (Leukotriene or Corticosteroid or Corticosteroid–Salmeterol; NCT 00156819) study (97).

Other regular daily treatments including oral therapy. Non-ICS strategies (e.g., long-acting antimuscarinic [LAMA] monotherapy) have been explored with conflicting results in patients with mild asthma. Although the SIENA study showed no significant difference in response for a composite outcome for either mometasone or tiotropium monotherapy in patients with low sputum eosinophils, compared with placebo (30), a recent cohort study saw increased exacerbations in patients treated with LAMAs without ICS (98). The latter study was limited by its retrospective nature and absence of lung function data (98). The role of LAMAs in adults with mild asthma could be explored in the future by stratifying for ipratropium bromide responsiveness or with the aid of biomarkers.

A meta-analysis of six studies of mild asthma concluded that LTRAs plus SABA relievers reduced exacerbation risk and improved lung function compared with a SABA alone (99). However, LTRA efficacy was lower compared with that of regular low-dose ICS, as confirmed in Cochrane meta-analyses (100). In the LOCSS step-down trial in mild asthma, LTRAs showed higher rates of treatment failure compared with ICS regimens (97). However, a randomized pragmatic study in mild asthma showed that initiation of LTRAs was as effective as initiated low-dose ICS in terms of asthma control and QOL in a real-life setting over a 2-year period (101), suggesting the need for further evaluation.

Theophylline is not recommended in mild asthma, because of side effects and a lack of efficacy compared with ICS (102).

As-needed use of ICS taken with a bronchodilator for symptom relief. As-needed ICSs were evaluated with rapid-acting bronchodilators in three different regimens: *1*) as-needed ICS plus formoterol (LABA) in a single inhaler, *2*) as-needed ICS plus albuterol (SABA) in a single inhaler, and *3*) as-needed ICS plus albuterol in separate inhalers.

Low-dose ICS–formoterol taken as needed for symptom relief was investigated in six randomized controlled trials (103). As-needed ICS–formoterol reduced the risk of severe exacerbations by 60–64% compared with as-needed SABA (21, 91). Compared with regular ICS, the severe exacerbation risk with as-needed ICS–formoterol was similar (21, 22) in blinded studies or lower in open-label pragmatic trials (67, 91), possibly related to poorer adherence to regular ICS. In the meta-analysis, the risk of emergency department presentation/hospitalization was 37% lower with as-needed ICS–formoterol versus regular ICS plus as-needed SABA (103).

As-needed ICS–formoterol was as effective as daily ICS for reducing exercise-induced bronchoconstriction (104). The reduction in severe exacerbations with as-needed ICS–formoterol compared with regular ICS (or SABA alone) was independent of baseline characteristics (high or low T2 markers, low or normal lung function, with/without exacerbation history, or with symptoms daily or twice per week or less) (18, 67, 91). Qualitative research demonstrated that as-needed ICS–formoterol was preferred by most patients with mild asthma, but shared decision making is needed (105).

Another intermittent therapy, albeit with less evidence, is to administer ICS whenever a SABA is taken using separate or combination inhalers. In the BEST study, the as-needed combination ICS–albuterol group had fewer exacerbations and higher peak flow than those receiving SABAs alone (90). In the BASALT (Best Adjustment Strategy for Asthma in the Long Term) study, exacerbation outcomes were similar with concomitant as-needed SABA and ICS (in separate inhalers) compared with physician adjustment or F_{ENO}-based adjustment of ICS dose every 6 weeks (106). Albuterol–ICS can also be used before exercise in adults with exercise-induced asthma or bronchospasm (107). Finally, a recently published pragmatic trial in Black and Hispanic uncontrolled asthma populations with high SABA use demonstrated that the instruction to use one inhalation of ICS with each inhalation of SABA, or five inhalations of ICS with each nebulized treatment of SABA in addition to their maintenance asthma medications, resulted in a significant reduction in severe exacerbation rates compared with usual care (108). Further research in the mild asthma population is needed given encouraging results with combination ICS/SABA reliever therapy in more severe disease (109). The U.S. Food and Drug Administration recently approved the use of as-needed combination albuterol–budesonide in asthma. Strategies that leverage patient behavior with a desire to take medication for the relief of acute symptoms and only when symptoms are present are critical in improving asthma

outcomes, as low adherence to maintenance therapies is well recognized in asthma, and the risks of unopposed SABA have been noted.

Other Potential Therapies for Mild Asthma

Given exacerbation risk in mild asthma (110, 111), research is needed to investigate the potential role of biologic therapies in asthma considered "mild" by daily symptoms and preserved lung function but associated with an elevated risk or history of a serious exacerbation, even after confirmation of good adherence. Omalizumab is a potential option, considering the prevalence of atopic mild asthma (28) and that the pivotal regulatory trials were in participants treated only with ICS (112, 113). Furthermore, despite prior underwhelming results (114), anti-IL–5, anti–IL-4Rα, and even anti–TSLP (thymic stromal lymphopoietin) biologics could be considered for research in this population, as 30–40% of patients with mild asthma demonstrated blood eosinophil counts >300 cells/μl (30, 92). In a study of patients with mild allergic asthma undergoing inhaled allergen challenge, treatment with tezepelumab normalized baseline blood and sputum eosinophils and $F_{E_{NO}}$ after a single dose and significantly diminished AHR before the subjects underwent allergen challenge, suggesting a future role for targeted therapy even in mild asthma (115). These concepts are speculative and clearly require further study, including an in-depth pharmacoeconomic analysis.

AIT involves the regular administration of gradually increasing doses of allergen extracts over a period of years. AIT changes the way the immune system reacts to allergens by switching off allergy and inducing allergen tolerance. It can be administered by subcutaneous injection or in sprays, drops, or wafers sublingually. A Cochrane review of subcutaneous immunotherapy in asthma showed significant reductions in asthma symptom scores and medication use and alleviation of AHR (116). The number needed to treat with immunotherapy to avoid one deterioration in asthma symptoms is 3 (95% confidence interval, 3–5). Sublingual immunotherapy has not demonstrated consistent benefit, and there is a lack of studies reporting important patient-specific outcomes, such as exacerbations and QOL (117). There are many small studies but very few rigorous randomized trials exploring AIT, and the role of sublingual immunotherapy remains unclear (Table 5).

NPIs for Mild Asthma

NPIs such as trigger avoidance, smoking cessation, inhaler technique and adherence, healthy diet, and physical exercise have been a consistent part of asthma guidelines (10). Unfortunately, the evidence for many NPIs is of low quality. This gap is further amplified by issues relating to sampling bias, blinding, finding appropriate control subjects, a large placebo effect from NPIs, and understanding the best outcome to measure with NPIs.

Although there is a paucity of recent and relevant research on NPIs for mild asthma, two interventions appear promising: aerobic exercise training (118) and breathing exercises (119). Varying aerobic exercise programs improved asthma control and lung function. In one small study, aerobic exercise appeared to improve asthma control in mild asthma, although there was a large possible placebo effect in the control group (120). It is estimated that ∼30–60% of patients with asthma have dysfunctional breathing, with hyperventilation being the most common pattern. In patients with mild to moderate asthma, breathing exercises (such as yoga, breathing retraining, and Buteyko and deep diaphragmatic breathing) appear to have benefits for QOL (Asthma Quality of Life Questionnaire) and hyperventilation scores (Nijmegen questionnaire) (121). A randomized controlled trial of two physiologically different sets of breathing exercises in patients with mild to moderate asthma demonstrated similar benefits on multiple outcomes, including a substantial reduction in SABA use (122). Another area of interest in asthma is weight loss. Although there are many questions about the design of future weight-loss studies, it is important to note that with increasing age, the adverse influence of obesity on the asthma phenotype is generally reduced (123). Hence, future trials should factor in effects by age groups.

There are other NPIs that need to be explored further in mild asthma, such as optimization of comorbid conditions and modification of diet. For example, the importance of treating anxiety and/or depression in patients with mild asthma by pharmacotherapy and/or CBT remains unclear (124). It does appear that targeted CBT addresses disease-specific anxiety symptoms, especially in patients with high baseline anxiety scores (125). Studies of pharmacotherapy in asthma have primarily targeted patients with depression but did not address those with anxiety as the main symptom. These small studies found either trends or improved asthma control in those with severe depressive symptoms. Similar comorbidities that mimic or aggravate mild asthma include gastroesophageal reflux disease and sinus disease, although their role in mild asthma needs to be better explained. There is also a lot more scope for elucidating the role of many dietary contributors (of a nonallergic kind, natural antiinflammatory) to mild asthma beyond targeting weight loss (126). This is a topic of great interest to members of the wider public who do not want to take medications and would welcome natural therapies or interventions, especially for mild asthma (127, 128). Further work should be considered in this area. Other promising NPIs may include well-designed patient education programs and multifaceted NPIs (e.g., those involving social workers, health visitors, and community health agents). In summary, there are multiple NPIs that warrant further investigation in mild asthma, as they are appealing to patients and hold the potential to control asthma without unnecessary medication exposure (Table 6).

Pediatric Research Needs in Mild Asthma

Diagnosis of Pediatric Mild Asthma

As in adults, there remains no universally accepted definition of mild asthma in children and adolescents (<18 yr of age). Although NAEPP divides mild asthma into intermittent and persistent disease, GINA does not, as even children with infrequent symptoms remain at risk of severe exacerbations (10). As in adults, GINA follows the ATS/ERS approach of defining mild asthma as that which is effectively managed with GINA step 1 or 2 therapeutic approaches.

There is substantial heterogeneity among children with mild asthma (129). Although many children can have features consistent with T2-high disease, a substantial proportion demonstrate little evidence of underlying atopy/T2 inflammation (130).

Functional lung changes can be detected even in children with mild asthma, as reflected by ventilation defects quantified by ^{129}Xe magnetic resonance imaging (131). Finally, the adverse long-term outcomes of

Table 5. Research Needs for Mild Asthma Treatments

Knowledge Gaps
Optimal treatment of patients who have symptoms only with URIs, or seasonal asthma, or with allergen or specific environmental exposure (including thunderstorm asthma, air pollution, weather events, stress)
Clinical features and biomarkers that predict treatment intensity required to achieve control in treatment-naive patients with mild asthma
Treatment options for patients who have difficulty perceiving bronchoconstriction ("underperceivers") or those who feel symptoms with slight change in lung function ("overperceivers")
Assessing symptom control when the reliever contains the patient's controller treatment
Differential effectiveness of therapies for reducing exacerbations in patients with mild asthma
When step up to maintenance and reliever therapy should occur in patients on ICS–formoterol reliever
Role of F_{ENO} in guiding therapy for well-controlled mild asthma (including patients with preserved lung function and low exacerbation frequency)
The safety and efficacy of as-needed ICS–SABA compared with SABA alone or as-needed ICS–formoterol or maintenance ICS plus as-needed SABA (particularly with frequent use)
Role of novel targeted therapies including biologics in mild asthma
Further understanding of allergen immunotherapy in mild asthma: timing, outcomes, and patient selection
Controller treatment options for patients who receive their relievers by nebulizer
Asthma action plan options for patients using as-needed ICS plus rapid-acting bronchodilator regimens
Suggested Research
Identify patients who need daily ICS-containing treatment, rather than ICS used whenever an as-needed reliever is taken
Determine if ICS-containing treatment is required in all populations with mild asthma
Identify populations that will benefit most from ICS therapy in terms of exacerbation reduction and symptom control
Conduct real-world and long-term follow-up studies evaluating the efficacy and safety of as-needed ICS plus rapid-acting bronchodilator regimens
Evaluate the benefits of ICS therapy in patients with elevated F_{ENO} concentrations but otherwise controlled mild asthma
Identify whether treatment strategies should differ between adolescents and adults
Identify predictors of treatment response in mild asthma and whether the predictive value of T2 biomarkers varies depending on the criteria chosen to define ICS response
Evaluate the safety and efficacy of as-needed ICS–SABA compared with SABA alone, vs. as-needed ICS–formoterol, vs. maintenance ICS plus as-needed SABA in patients with newly diagnosed asthma and patients with mild asthma
Investigate fluticasone furoate–LABA (which has a prolonged duration of antiinflammatory effect) for twice-weekly use as a step-down option compared with continuing daily treatment.
Assess the efficacy and safety of stepwise algorithms across the range of asthma severity, including mild asthma
Investigate how beliefs and behaviors about SABA-only treatment (among patients, clinicians, and policy makers) can be changed and how to communicate the importance of population-level risk reduction strategies when symptoms are infrequent
Explore the effect of biologics in well-characterized patients with mild asthma, to identify those who may benefit from early introduction of therapy (e.g., by identifying biomarkers for relative corticosteroid refractoriness)
Standardize outcomes for studies of allergen immunotherapy using validated scales and exacerbations as end points
Characterize the patients with mild asthma who respond best to allergen immunotherapy
Conduct head-to-head comparative studies to assess the size of effect of allergen immunotherapy compared with other therapies

Definition of abbreviations: F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; LABA = long-acting β-2 agonist; SABA = short-acting β-2 agonist; T2 = type 2; URI = upper respiratory infection.

mild to moderate childhood asthma on lung growth have been clearly demonstrated through follow-up of the CAMP (Childhood Asthma Management Program) cohort, showing that three-fourths of children with mild to moderate asthma demonstrate abnormal patterns of lung growth with reduced growth and/or early decline in FEV_1 (132).

Overall, mild asthma represents a substantial proportion of childhood asthma, with significant associated morbidity. As in adults, better strategies to better define mild asthma are needed in children, as well as well-designed clinical trials to determine optimal management strategies to minimize short-term symptom burden, maximize QOL, and reduce the risk of long-term impacts on lung growth.

New Approaches to Using Approved Medications for Treatment of Mild Pediatric Asthma

There are several ICS-based strategies endorsed by the NAEPP guideline (18) and GINA statement (10) using approved medications in children with mild persistent asthma. Low-dose ICS is effective in controlling symptoms in children with asthma. In the 5- to 44-year age group, ICS reduced hospitalization risk by 31% in those who used at least one canister of ICS during each of the four quarters of the year (133). Furthermore, there was a progressive decline in mortality risk with increasing ICS use, with a decrease of more than 50% with the use of more than six ICS canisters annually (134). Low-dose ICS reduced the risk of a serious exacerbation (admission, emergency treatment, or death) by 44% (135). Severe exacerbations requiring systemic corticosteroids were reduced by 0.48 in children and adults with 0 or 1 symptom day per week, prebronchodilator lung function was higher, and symptom-free days were more frequent (20) Similar results have been observed in persistent versus intermittent asthma (20).

Table 6. Research Needs for Nonpharmacological Intervention in Mild Asthma

Knowledge Gaps
Effects of aerobic exercise in mild asthma
Effects of different breathing techniques in mild asthma
Better understanding of other nonpharmacological interventions such vaping or smoking cessation
Short-term and long-term benefits of diet (not targeting weight loss) and antioxidant foods
Influence of comorbidities on the mild asthma symptom burden (anxiety, depression, sinus disease, and GERD)
Suggested Research
Evaluate the efficacy of aerobic exercise programs in mild asthma
Assess long-term outcomes of different breathing exercises in patients with mild asthma, particularly in those with suspected dysfunctional breathing
Evaluate the short-term and long-term benefits of diet and antioxidant foods in obese and nonobese patients
Evaluate the benefit of weight loss in obese patients with mild asthma and whether benefit varies by age group
Evaluate CBT and pharmacotherapy in patients with mild asthma and concomitant anxiety and/or depression
Evaluate the benefits of therapeutic patient education (including a written action plan) in mild asthma

Definition of abbreviations: CBT = cognitive behavioral therapy; GERD = gastroesophageal reflux disease.

In preschool-aged children with intermittent wheezing at high risk to develop asthma, the use of daily ICS (136) and intermittent high-dose ICS (137) was associated with decreased symptoms and exacerbations. Moreover, preschool-aged children with mild persistent asthma with markers of T2 inflammation, such as aeroallergen sensitization or a blood eosinophil count of >300 cells/μl, showed a differential response favoring daily ICS compared with LTRAs or ICS taken whenever albuterol was used for symptoms (138).

In adolescents aged 12–17 years with mild asthma, as-needed budesonide–formoterol was superior to as-needed terbutaline for severe exacerbation reduction, with similar efficacy to budesonide maintenance (139). Adherence to controller medication is key to asthma control, and the as-needed controller approach may improve adherence when it is most needed, during a period of increased symptoms.

A recent meta-analysis of nonpharmacological approaches for children and adults demonstrated that patient education programs, multifaceted interventions, renovating homes to reduce environmental exposures, and air filtration systems significantly improved asthma control (140). In addition, the psychosocial environment is recognized as a significant contributor to asthma morbidity. It includes a person's neighborhood, socioeconomic status, family relationships, and social

Table 7. Research Needs for Pediatric Mild Asthma

Knowledge Gaps
Definition of mild asthma in the pediatric population
Mild asthma phenotyping in children
Risks of disease progression in mild asthma in children
The effects of exacerbations and associated risks in children with mild asthma
Role of as-needed ICS inhalers in children
Better understanding of social determinants of health in pediatric mild asthma
Suggested Research
Determine the best definition of mild asthma in the pediatric population
Determine the best approaches for the early detection of children at risk of progression from mild to more severe asthma and whether interventions can alter this progression
Evaluate whether personalized treatment strategies on the basis of a phenotype or an endotype approach lead to improved treatment response
Evaluate the efficacy and safety of as-needed ICS, either alone or in combination with SABA or formoterol, in children with mild asthma
Evaluate the long-term consequences in terms of exacerbation risk and lung growth with intermittent or as-needed ICS plus rapid-acting bronchodilator use compared with daily ICS plus a bronchodilator
Evaluate whether social supports and services as well as law and policy changes result in improved asthma outcomes
Evaluate the impact of patient-oriented and health services research on positive change in home and community environmental conditions and its effectiveness to improve asthma outcomes in pediatric asthma

Definition of abbreviations: ICS = inhaled corticosteroid; SABA = short-acting β-2 agonist.

Table 8. Patient and Caregiver Comments

On the Definition of Mild Asthma
"A patient [who] does not go to the urgent care or have hospitalizations. Does not need a maintenance inhaler daily—rescue inhaler expires before it is used."
"A patient [who] does not go to the urgent care or have hospitalizations. Does not need a maintenance inhaler daily—rescue inhaler expires before it is used."
On Concerns Relating to Mild Asthma
"A concern is the price of the medication. Because of cost, you may not feel like you need it till you ACTUALLY need it."
"They are more likely to forget to take their inhaler [rescue] when they are outside. For example, while camping. More likely to forget because they do not use maintenance inhalers."
"We did not take inhalers till WE FELT the inhaler made a difference regardless of what we were prescribed."
"These patients are less cognizant about their symptoms. They are not in tune with their symptoms. They blame it on obesity/deconditioning and so on."

networks (141–144). Structural discrimination can influence asthma, as it can manifest as unequal access to high-quality medical resources, substandard housing, lack of homeownership, and living in neighborhoods with higher amounts of pollution (144). Home ownership was associated with lower odds of an asthma emergency department visit (Table 7) (144).

Patient Perspective on Mild Asthma

The patients and caregivers agreed that more research is needed in mild asthma. Some of their comments are represented in Table 8. We presented three fictional cases with mild asthma (one child and two adults) to set the stage for this discussion and asked the participants to determine if they considered that the cases represented mild asthma and to identify the key factors that should be included for the definition of mild asthma from their perspective. Patient views of the definition of mild asthma differed from person to person. However, there was consensus that individuals with mild asthma should not have high healthcare use, high symptom burden, or high medication need.

The patient panel noted that symptom thresholds were an important part of the definition of mild asthma, but they expressed different views of the meaning of mild. The duration, severity, and frequency of symptoms were important to the healthcare providers on the panel (*see* Table E5), and patients wondered how seasonal variability in disease would be taken into consideration.

The general sentiment was that daily maintenance medication use was an indicator of the presence of moderate or severe asthma. Interestingly, patients shared concerns about the challenges of defining mild asthma in the setting of background inhaler use. They conceded that it is hard to compare control in patients who are on maintenance therapy with those who are treatment naive.

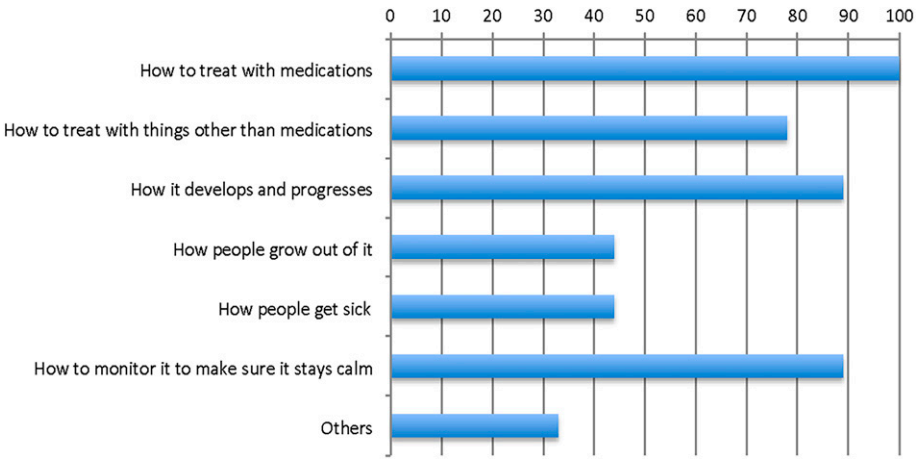

Figure 2. Research priorities in mild asthma from a patient's perspective.

What Are the Concerns for Patients with Mild Asthma?

All patient panel members stated that there are several concerns and challenges that are unique to patients with mild asthma. These concerns included issues with underrecognition of the disease as well as a lack of awareness that leads to the disease not being taken seriously by both patients and healthcare providers.

Several reasons for medication nonadherence in this population were identified. They included concerns about medication costs, forgetting to take medications, and a perceived lack of benefit of the prescribed therapies. In patients with mild disease, there is a tendency to underrecognize asthma symptoms and a lack of awareness of the seriousness of the disease. A patient shared her story about not recognizing symptoms related to asthma while she was in college until she finally received a diagnosis of asthma. Several members mentioned that both doctors and patients do not take mild asthma seriously until they end up in the emergency department. This may be due in part to a lack of education or training in patients with mild compared with severe asthma. In addition, those with mild disease may not receive education regarding disease control measures and medications because of the presumption that their disease is not serious. An example of lack of appropriate education noted was the discrepancies in the use of asthma action plans in the United States compared with other countries.

On What Should Research on Mild Asthma Focus?

Each panel member was asked to identify priority areas for research in mild asthma. Panelists were instructed to both select research topics from a list and make

Table 9. Research Needs from the Patient Perspective in Mild Asthma

Knowledge Gaps
Patients' concerns with mild asthma
Patient opinions about needs for future research, including *1*) the role of peak flow meter and spirometry monitoring; *2*) the effect of anxiety in patients with mild asthma; *3*) the impact of healthcare disparities on the care of patients with mild asthma; *4*) closing diagnosis gaps in mild asthma; *5*) epidemiology studies, including those focused on remission; and *6*) effective biomarkers to assess disease control
Suggested Research
Evaluate patient education that specifically targets patients with mild asthma
Define symptom severity and frequency in a way that helps patients recognize and treat their asthma optimally
Investigate medication adherence strategies for mild asthma that can help patients who are prescribed daily treatment be motivated to maintain their antiinflammatory treatment
Investigate whether nonpharmacological interventions can help reduce medication requirements in patients with mild asthma (such as anxiety and monitoring [e.g., peak flow])

specific recommendations (Figure 2). There was consensus from all members that more research on how to treat patients with mild asthma with medications was required (100%). In addition, research should focus on how mild asthma develops and progresses (89%) and how to monitor it and achieve optimal control (89%), and then how to treat mild asthma with NPIs (79%). Lower priority topics were asthma initiation (44%) and remission (44%).

Specific suggestions were obtained, including focusing on improving symptom recognition and providing more effective patient education because of limited knowledge of the disease. The education would focus on a variety of topics, including symptom recognition, inhaler technique, and the natural history of the disease. There was also an interest in identifying patients who would be appropriately treated with as-needed ICS versus maintenance therapy. Other research topics include *1*) the role of peak flow meter and spirometry monitoring; *2*) the effect of anxiety in patients with mild asthma; *3*) the impact of healthcare disparities on the care of patients with mild asthma; *4*) closing diagnosis gaps in mild asthma; *5*) epidemiology studies, including those focused on remission; and *6*) effective biomarkers to assess disease control (Tables 8 and 9).

Conclusions

There are multiple knowledge gaps and unmet research needs in mild asthma. An important first step is to develop a robust definition that reflects its epidemiology, heterogeneity, and associated risks. Next, we must develop dedicated research constructs, independent of other severity groups, to explore its pathophysiology and management. Wherever applicable, findings must be evaluated by age group. We must also acknowledge the needs of at-risk individuals and special populations within this group. Our statement represents an important first step but is not exhaustive. We strongly advocate for greater funding and prioritization of research on mild asthma and encourage engagement with all stakeholders, including patients and caregivers. ■

This official research statement was developed by an *ad hoc* subcommittee of the ATS Assembly on Allergy, Inflammation, and Immunology.

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