Supplement

New and Anticipated Therapies for Severe Asthma

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INFORMATION FOR CATEGORY 1 CME CREDIT

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Stephen P. Peters, MD and William W. Busse, MD (authors); Jessica Martin (medical writer); Michael Schatz, MD, MS (editor); Samuel Gubernick, DO and Brian T. Kelly, MD (reviewers)

Learning objectives:

1. To recognize that asthma remains uncontrolled in a significant number of patients, due to uncertainty about the definition of control and severity, and multiple barriers to effective follow-up.

2. To utilize current evidence-based practice guidelines and strategies to improve asthma control in patients with severe asthma.

3. To integrate novel and emerging drugs into recommended and properly applied management strategies for asthma control in patients with severe asthma.

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Asthma is frequently undertreated, resulting in a relatively high prevalence of patients with uncontrolled disease, characterized by the presence of symptoms and risk of adverse outcomes. Patients with uncontrolled asthma have a higher risk of morbidity and mortality, underscoring the importance of identifying uncontrolled disease and modifying management plans to improve control. Several assessment tools exist to evaluate control with various cutoff points and measures, but these tools do not reliably correlate with physiological measures and should be considered a supplement to physiological tests. When attempting to improve control in patients, nonpharmacological interventions should always be attempted before changing or adding pharmacotherapies. Among patients with severe, uncontrolled asthma, individualized treatment based on asthma phenotype and eosinophil presence should be considered. The efficacy of the anti-IgE antibody omalizumab has been well established for patients with allergic asthma, and novel biologic agents targeting IL-5, IL-13, IL-4, and other allergic pathways have been investigated for patients with allergic or eosinophilic asthma. Fevipiprant (a CRT_H2 [chemokine receptor homologous molecule expressed on Th2 cells] antagonist) and imatinib (a tyrosine kinase inhibition) are examples of nonbiologic therapies that may be useful for

Abbreviations used
DDP-4- dipeptidyl peptidase 4
FENO- fraction of exhaled nitric oxide
GINA- Global Initiative for Asthma
ICS- inhaled corticosteroid
LABA- long-acting beta$_2$ agonist
SABA- short-acting beta$_2$ agonist
TSLP- thymic stromal lymphoprotein

patients with severe, uncontrolled asthma. Incorporation of new and emerging treatment into therapeutic strategies for patients with severe asthma may improve outcomes for this patient population. **(J Allergy Clin Immunol Pract 2017;5:S15-S24)**

Key words: *Asthma; Control; Biologics; Eosinophilic asthma; Severe asthma; Uncontrolled asthma*

Asthma is a chronic respiratory disease characterized by inflammation and narrowing of the airways that leads to breathlessness and wheezing. According to the World Health Organization, asthma is one of the most common noncommunicable diseases worldwide, affecting approximately 235 million people. The Global Asthma Network, however, estimated in 2014 that the number of people affected by asthma worldwide may be as high as 334 million.[1] Asthma is also responsible for approximately 250,000 premature deaths each year, caused by various factors, most of which are preventable.[2]

Since 1995, the Global Initiative for Asthma (GINA) has published comprehensive reports intended to facilitate and guide treatment of this heterogeneous disorder. The GINA reports influence national and international clinical practice guidelines and have evolved in terms of recommendations and approaches to asthma treatment based on new information and research. Over the last 2 decades, our understanding of asthma has improved substantially. Consequently, the field has seen great advances in terms of medications as well as the genetic, environmental, and psychosocial factors that contribute to asthma and its control. In 2006, the GINA report was revised to emphasize the importance of asthma control, representing a major shift in asthma classification that distinguished asthma control from severity.[3] Although this was an important shift in thinking, only recently has the heterogeneity of asthma been well appreciated, and new medications and treatment paradigms have led to the possibility of individualized therapy in some patients with severe or uncontrolled asthma. This research led to the most recent large-scale revision of the GINA report in 2015, which provides practical clinical guidance toward asthma control worldwide.[4] Since then, GINA has released yearly updates to its asthma documents based on recent data.

Although asthma may be a highly treatable disorder with various resources and therapies available to physicians and most patients, many patients still suffer from ongoing symptoms and exacerbations, indicating suboptimal asthma control. In that regard, recent multinational surveys indicate that between 38% and 54% of patients with asthma have uncontrolled asthma.[5-8] In large part, the low rate of asthma control may be due to factors that are modifiable by nonpharmacological means—treatment adherence, inhaler technique, and allergen exposure.[9-11] For many patients with uncontrolled asthma, however, stepped up pharmacological interventions or new approaches may be in order.

Novel and emerging asthma treatments have recently become available for patients who have more severe disease and need more intense therapy. In some cases, even after providing treatment that would appear to be optimal, some patients continue to present with uncontrolled symptoms and exacerbations. When this occurs, patients are considered to have severe asthma. Patients in whom asthma remains uncontrolled may be at high risk for death.[12] Fortunately, several of the new and emerging asthma treatments, many of which are biologic agents, have shown efficacy in patients in this subgroup.

Large administrative databases and data analyses allow identification of patients with severe, persistent asthma, making targeted treatment interventions feasible. Identification of high blood eosinophil count frequently correlates with future risk of exacerbations and excessive short-acting beta$_2$ agonist (SABA) use.[13-15] Early identification of patients with high blood eosinophil counts and/or uncontrolled asthma may lead to substantial cost savings as well as a reduction in health care utilization.[16,17] Administrative data gleaned through information pharmacy technology can also allow clinicians to monitor factors related to asthma control in real time, allowing clinicians to flag patients with excessive asthma medication use and consequent persistent asthma symptoms.[18] If used properly, administrative databases may improve the overall state of asthma control monitoring, allowing clinicians to identify patients who might be at risk for future exacerbations.

Guidance for the effective use of new therapies in patients with severe, uncontrolled asthma is, however, limited. The 2017 GINA guidelines do not comprehensively describe the incorporation of biologics into treatment regimens, and direct comparisons between these agents are not available. In addition, the European Respiratory Society/American Thoracic Society clinical practice guidelines have not been updated since 2014.

The goal of this review was to highlight the importance of identifying patients who suffer from uncontrolled asthma, review possible nonpharmacological interventions, and discuss currently available approaches for treating patients with severe asthma.

UNCONTROLLED, SEVERE ASTHMA: UNDERRECOGNIZED AND UNDERTREATED

The degree of control is an important consideration when assessing a patient with asthma. As defined by GINA, asthma control consists of 2 separate domains, symptoms (impairments) and future risks, including exacerbations and adverse outcomes. Assessment of symptom control includes a consideration of the presence of daytime asthma symptoms, use of reliever medications (use more than twice per week is suboptimal), nighttime waking due to asthma, and activity limitation due to asthma. Risk factors for future exacerbations include the presence of uncontrolled symptoms, unavoidable environmental exposures, severe disease, and comorbidities such as nasal polyps and sinusitis.[19]

Because of the substantial impact of asthma exacerbations and continual symptoms on patients' lives, patients with uncontrolled asthma experience considerable morbidity. Uncontrolled asthma contributes to impaired work productivity and higher rates of absenteeism from both school and work.[20,21]