Grant Request for Independent Learning and Change
Focus on Knowledge and Competence

From Cradle to Grave:
Controlling Severe Asthma Throughout the Lifespan

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Goals and Objectives

Goal: The goal of this educational initiative is to improve clinician knowledge and competence regarding current management options for severe asthma throughout a patient's lifespan.

Objectives: This educational initiative will focus on the following educational objectives:

1. Describe current phenotypes for severe asthma in both adults and children
2. Discuss the role that phenotypes play in the management of severe asthma in adults and children
3. Analyze the clinical applicability of the ERS/ATS task force guidelines and how these can be applied to the treatment of specific asthma phenotypes
4. Summarize targeted biological drug therapy and assess ways to correctly use currently-available and emerging agents in clinical practice for adults and children with severe asthma

Assessment of Need

Overview

Asthma is considered a chronic inflammatory airway disease often characterized by recurrent episodes of wheezing, cough, and/or breathlessness. During these episodes, airflow obstruction is often reversible, either spontaneously or with treatment. However, many individuals diagnosed with asthma have progressive or fixed airway obstruction as well as increased bronchial hyperresponsiveness to a variety of stimuli that complicate their condition.

According to the Centers for Disease Control and Prevention, 25.7 million individuals in the United States had been diagnosed with asthma as of 2010, an increase of nearly 22% in just a single decade. Of this total, about 18.7 million were adults and 6.8 million were children, representing 8.4 percent of the total U.S. population. (CDC)

The prevalence of asthma is highest in the northeastern and northwestern United States, topping 10 percent of the total adult population in many states. The prevalence is at least 6 percent in each of the 50 states, but it generally is lowest in the southeast. (CDC)

On an annual basis, asthma accounts for 14.2 million outpatient visits, 1.8 million emergency room visits and 439,000 hospitalizations. In addition, there were 3,630 deaths attributed to asthma in 2013. (CDC)

There is no single contributing factor that leads to asthma, although a number of genetic and environmental triggers may put an individual both at risk of developing asthma and exacerbations of their condition. Environment and epigenetic risk factors such as prenatal influences, respiratory infections, allergens, tobacco smoke, air pollutants, diet, and other factors have all been found to impact the development and severity of a patient's asthma.

Despite available treatments, asthma remains poorly controlled in a large percentage of the population. While down from 2001, the number of adults and children who reported at least 1 asthma attack in 2010 remained high, hovering near 50% in adults and almost 60% in children.

About 1 in 2 children with asthma miss 1 or more school days each year, and about 1 in 3 adults miss at least 1 day of work. Even when individuals with asthma avoid having an attack, many report physical limitations, with about 60 percent of asthmatics saying that they limit their usual activities because of the condition. Based on these statistics, the management of asthma – particularly in its most severe stages – clearly is in need of improvement.

Educational Gap 1: As more is being learned regarding common symptoms and characteristics of asthma, clinicians are being challenged to reach beyond the simple categorization of mild, moderate, and severe asthma and break patients into more distinct clusters that affect their overall management strategies.

Accurately classifying the severity of asthma is important for managing asthma and assessing patients' long-term risk. Traditionally, asthma has been divided into mild, moderate, and severe categories based on a patient's symptoms, lung function, and the frequency of short-acting bronchodilator use. Based on this categorization, treatment is then tailored to the patient's needs. However, this approach does not adequately take into consideration the heterogeneity of asthma that is observed clinically in many patients. It also implies the incorrect assumption that all patients within the same severity classification will respond similarly to the recommended medications for that class.[2] This assumption is especially flawed in patients with severe asthma, who consist of only 5-10% of asthmatic patients but account for the majority of healthcare costs related to treatment.[3]

In order to improve long-term outcomes for patients with severe asthma and make treatment more patient-specific, several studies have sought to improve the classification of severe asthmatics.[4] The largest of these to date – the Severe Asthma Research Program (SARP) -- established 5 unique cluster types in adult asthma patients (>12 years) based primarily on clinical characteristics. The age of disease onset, lung function, and the presence of atopy are all significant features of the defined clusters.

The clusters are broken down in the following general manner:[2]

- **Cluster 1**: Typically female, early-onset atopic asthmatics with normal lung function, treated with up to two controller medications, and minimal healthcare utilization
- **Cluster 2:** Predominantly female, early-onset atopic asthmatics with preserved lung function but increased medication requirements and healthcare utilization
- **Cluster 3:** Older obese women with late-onset non-atopic asthma, moderate reductions in FEV_1, typically requiring 3 or more maintenance medications, and frequently require oral corticosteroids
- **Cluster 4 and 5:** Asthmatics with severe airflow obstruction but variability in responsiveness to bronchodilators, age at asthma onset, atopic status, and use of oral corticosteroids

There are, quite clearly, overlapping characteristics within each of these clusters, although taken in sum, the specific symptoms within each cluster suggest different pathophysiologic processes that may determine therapeutic response and thus affect asthma control.

Another study based in Leicester, U.K. utilized sputum eosinophil counts to define four separate clusters of severe asthmatics. These clusters were similar to those in the SARP study and included early onset atopic-asthma, non-eosinophilic asthma in obese patients, early-onset asthma with significant symptoms, and later-onset, inflammation -predominant asthma.[5]

Cluster groups have also been identified in children with severe asthma. The SARP study identified 4 clusters in children ages 6 to 17 that included the following:

- **Cluster 1:** Late-onset with normal lung function and less atopy
- **Cluster 2:** Early-onset atopic asthma with normal lung function and increased medication use
- **Cluster 3:** Early-onset atopic asthma with mild airflow decrease
- **Cluster 4:** Early-onset with advanced airflow restriction and greatest medication use.[6]

However, asthma phenotypes or clusters in children do not appear to be as stable as they are in adults nor are they as predictable of clinical outcomes.[8,9] Because of this, less is known about how these phenotypes may be applied clinically for the treatment of asthma in children.

In addition to this clustering, research is ongoing into the identification of biomarkers to indicate the phenotype of patients who are likely to respond therapeutically to targeted treatment.[3] Two such biomarkers that have been identified are based on the presence of specific inflammatory cells -- eosinophilic and non-eosinophilic (neutrophilic) asthma. Each phenotype accounts for about 50% of asthma patients.

Patients that are considered eosinophilic have blood eosinophil counts greater than 220/mm.[10] They also exhibit higher levels of serum IgE and a greater degree of bronchial hyperresponsiveness.[11] This subgroup of patients has been found to respond well to inhaled corticosteroid (ICS) therapy. On the flip side, patients with low Th2 cytokines have little or no response to ICS treatment.

Knowing which subgroup a patient falls into can help clinicians determine how a patient may respond to ICS treatment, thus improving the use of targeted medications and reducing a patient's exposure to potential side effects from ineffective medications.

The noneosinophilic or neutrophilic asthma phenotype has also been described, although the underlying mechanism of action of this phenotype is less clearly understood. These patients express a sputum eosinophil count less than approximately 3% and a neutrophil count ranging from greater than 60% to 76%.[10,11]

The identification of phenotypes in severe asthmatics and the biomarkers associated with them is helping to drive the development of biological agents that target these biomarkers, particularly in adult patients. Clinicians must therefore be aware of these subsets so that targeted medications can be used effectively in appropriate patients.

Educational Gap 2: Clinical guidelines for the management of asthma do not appropriately reflect the heterogeneity of the condition within and across levels of asthma severity. The holes in these

guidelines are particularly important in patients with severe asthma who are typically the most difficult to treat successfully.

While efforts have been made to more accurately differentiate the signs and symptoms of asthma into individualized clusters, treatment guidelines are yet to catch up. For instance, the Expert Panel Report 3 of the National Asthma Education and Prevention Program recommends assigning disease severity into the more traditional following classifications: intermittent, persistent-mild, persistent-moderate, persistent-severe. These classifications are determined by reported symptoms, lung function, and the frequency of short acting bronchodilator (SABA) use.[12]

Similarly, the Global Initiative for Asthma (GINA) uses mild, moderate, and severe classifications. However, this system bases patient classification by the medications that are required to control their asthma.[13] This GINA system defines severe asthmatics as those that are refractory to asthma treatment and have comorbidities that may not be adequately treated.

Both of these guidelines fail to recognize the heterogeneity of asthma and make the assumption that ICS treatment -- the mainstay of treatment for both guidelines -- should be universally effective.[14] Not surprisingly, despite the wide use of these guidelines, the treatment of severe asthma continues to be a major unmet clinical need, as recently illustrated in a European study by Chung et al. This study assessed the cost of severe asthma by calculating the cost of medical treatment, lost productivity, and days lost from work. Patients with severe asthma that was not controlled required more than 4 times greater costs than well-controlled asthmatics.[15]

To address the need to match the improved understanding of the symptomatology of severe asthma and its management, the European Respiratory Society and American Thoracic Society (ERS/ATS) Task Force was created. Among other aims, this task force evaluated the role of asthma phenotypes and the clinical role they should play in patients with severe asthma. In a 2014 report, the task force acknowledged that while no specific asthma phenotypes have been widely accepted, identifying specific characteristics common to multiple phenotypes may help to direct therapy, especially as more knowledge is gained. Three common characteristics were recognized by the task force -- obesity, eosinophilic inflammation, and allergic/Th2 processes. The latter two were found to be particularly useful when considering corticosteroid and targeted therapies.[16]

According to the task force report, identifying patients with a later-onset eosinophilic phenotype may be useful in assessing the risk of exacerbations, predicting response to corticosteroids, and possibly predicting response to targeted therapy. It was recommended to measure sputum eosinophilic counts in adults to recognize patients in this category but not in children, whose results are less specific.[16] Because of the strong association between allergy and asthma in children, along with importance of eosinophilic counts in adults, the task force recommends that a trial of omalizumab be considered in adults and children older than 6 if serum IgE levels were between 30-700 IU/mL.[16] Newer treatments for patients with the eosinophilic phenotype have been approved by the FDA since the release of the task force's

guidelines and are therefore not included in their recommendations. This needs to be taken into consideration by clinicians managing severe asthmatic patients.

The ERS/ATS task force is the first to provide guidelines regarding the role of asthma phenotypes and their clinical application in both adults and children. As noted by Guy Brusselle, MD, Guidelines Director for the European Respiratory Society, "These new guidelines provide recommendations for an approach to diagnose and treat the condition, and it's our responsibility to now ensure they are implemented for the benefit of patients."[31] Additionally, Gary Walsh, MD, indicated that the guidelines presented by the task force are key to moving the field of asthma treatment forward and will help lead to personalized therapy.[17] It is therefore critical to improve clinicians' knowledge of and use of these guidelines.

Educational Gap 3: The rise of targeted therapy for the management of severe asthma is complicating the clinical decision making process, while offering patients new options for improvements in therapy.

As more is understood about the pathophysiology of asthma, new treatments have been developed that target both IgE and components of the Th2 pathway (IL-4, IL-5, IL-13), which are important for eosinophil production and function.[4] When biologics were initially tested in all severities of asthmatics, the results were disappointing. However, when patients with specific phenotypes were selected for testing, they often had a measurable clinical improvement compared to placebo. Proper patient selection for biologic drugs is proving to be the key for their success.

The first biologic to gain FDA approval was omalizumab, a humanized antibody that binds to circulating free IgE. Omalizumab is currently the only biologic medication approved for use in both adults and children >age 6 with moderate-to-severe allergic asthma, elevated serum IgE, and incomplete control with conventional therapy.[18] Response to omalizumab has been difficult to predict, but it appears to be most successful in patients with elevated eosinophil levels.[19] Because of an FDA black box warning due to the potential for anaphylaxis, omalizumab is recommended for use as a subcutaneously-injected medication in the office setting only.[20]

> "These are exciting times as new therapeutics emerge along with a greater mapping of mechanistic characteristics of an individual patient's asthma, their endotype. As these fields of knowledge merge, effectiveness and precision of treatment will follow, providing patients and physicians with a greater promise for disease control and eventual march to a cure."[32]

IL-5 is key to the growth of eosinophils, differentiation, and migration into sites of asthmatic inflammation, and has proven to be an effective target for a subset of severe asthma patients.[21] Two anti-IL-5 monoclonal antibodies -- mepolizumab and reslizumab -- are currently approved for the treatment of eosinophilic asthma subtypes. Benralizumab, an anti-IL-5 receptor alpha antibody, is currently undergoing clinical trials.

Mepolizumab was approved by the FDA in November 2015 for use as add-on, maintenance treatment in patients ≥12 years who have an eosinophilic phenotype. Side effects include hypersensitivity to the subcutaneous injection and herpes zoster infections.[22] When mepolizumab was initially studied in patients with mild asthma, it did not show a reduction of eosinophils in the airway nor did it improve lung function.[23] Only when mepolizumab was studied in patients with severe, uncontrolled asthma with high eosinophil counts was a reduction in eosinophil counts seen, along with a reduction in the number of exacerbations and improved quality of life when compared to placebo.[24] This finding has been confirmed in several studies.[25,26] The possible role of mepolizumab in children ages 6 to 11 is currently being evaluated in an open-label clinical trial.[31]

Reslizumab was approved in March 2016 by the FDA as add-on, maintenance therapy for severe asthmatics ≥18 years who have an eosinophilic phenotype. Anaphylaxis is a rare but serious side effect of reslizumab, so it is given only in clinical settings that are prepared to manage anaphylaxis.[27] Similar to mepolizumab, patients with poorly controlled asthma and elevated blood eosinophil counts treated with reslizumab have shown an improvement in the number of asthma exacerbations when compared to placebo. Improvements in lung function and quality of life were also seen.[28]

Benralizumab, which is currently being studied in phase 3 trials, differs from mepolizumab and reslizumab by targeting the IL-5 receptor alpha antibody. A recent phase 2b study in adult asthmatics with eosinophilic, uncontrolled asthma treated with benralizumab showed a reduction in asthma exacerbations and baseline blood eosinophils.[29] A phase 3 study of this medication was recently completed, with results pending.

Other agents currently in late-stage clinical trials include dupilumab, an anti-IL-4 receptor antibody that blocks both Il-4 and Il-13 signally. Recent results from a phase 2b study in adult asthmatics with poorly controlled asthma and elevated eosinophils who were treated with dupilumab showed an increase in lung function and a reduction in exacerbations compared to placebo.[30] Several drugs that target IL-13 are currently undergoing clinical trials but results have been variable to date.

These are exciting times as new biologic medications for the treatment of asthma become available for the treatment of asthma. As more becomes known about individual patient phenotypes, Drs. J. Darveaux and W. Busse predict that the “effectiveness and precision of treatment will follow, providing patients and physicians with a greater promise for disease control and eventual march to a cure.”[32]

Summary

Severe asthma is a complex, heterogeneous, chronic disease that is now recognized to be composed of several different phenotypes. While there are currently no universally recognized phenotypes, the ERS/ATS task force recently acknowledged obesity, eosinophilic inflammation, and allergic/Th2 processes as having clinical implications. Specifically, eosinophilic and allergic/Th2 processes have been the target of recent biologic agents. These targeted therapies have been found to be effective only in specific subsets of severe asthma patients, so an understanding of these subsets is key to their

appropriate use. New guidelines proposed by the ERS/ATS task force may help to define these subsets of patients.

While similar phenotypes have also been defined in children, these have proven to have fewer clinical implications because they appear to be less static in children compared to adults. As more becomes known about phenotypes in children, this is likely to change.

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