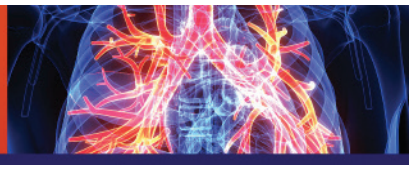
ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

EXPERT perspectives

Advancing Knowledge to Practice: Optimizing Severe Asthma Care in the Age of Biologics



Dear Colleague:

There have been numerous advances in the treatment of patients with severe asthma, yet unmet needs remain. These include having a better foundation of the pathophysiology of severe asthma and the ability to differentiate between targeted biologic agents and their specific pathway. There is also a need improve the selection of targeted biologic therapies for severe asthma based on phenotype and an improved ability to manage severe asthma in accordance with the latest guidance and novel therapies available. Please consider some key points from our certified, multidisciplinary, educational initiative, ***Advancing Knowledge to Practice: Optimizing Severe Asthma Care in the Age of Biologics***, in which we discuss how phenotype, eosinophils, available biomarkers, and other genetic characteristics factor into the management of severe asthma. In addition, this activity reviews the latest biological agents available in the treatment of severe asthma.

- Asthma is not a clinically homogeneous condition. There are many variances in clinical presentation and physiologic characteristics, which also determine how patients respond to various treatments. Clinicians need to consider the patient's **phenotype**, the outward manifestation of how a disease state presents as a combination of genetics and environmental influences. To understand a patient's asthmatic disease, a clinician also needs to look at the **endotype**, which is the underlying pathogenic mechanism of the patient.
- When discussing severity and treatment strategy of asthmatic patients, it is important to understand how to characterize a patient's clinical **phenotype**. A patient's phenotype includes the following characteristics:
    - Clinical or physiology characteristics, ranging from gender to age of onset of the disease, as well as the severity of the disease–referring to lung function or measure of airway hyperresponsiveness, and number of exacerbations
    - Asthma triggers, such as allergens, like pets, dust mites, and pollens
    - Sputum inflammation–both eosinophils and neutrophils–looks at cells to characterize which pathway is most involved in the person's individual asthma. For example, 2% sputum eosinophils establish asthma as an eosinophilic phenotype.
- The characteristics of phenotype and endotype influence proteins and biochemical pathways, as well as inflammatory cells, and may be best described in the following key subgroups for severe asthma:
    - **Endotype or key groupings of severe asthma**
        - **Early onset:** history of food allergy, atopic dermatitis, likely to develop allergic rhinitis and/or conjunctivitis before finally developing asthma
        - **Late onset:** minimally allergic or minimally atopic eosinophilic asthma; disease often follows severe bronchial infection, recurring sinus infections; often have chronic rhinosinusitis with nasal polyps; severe airways obstruction; exacerbation of nasal obstruction or asthma in response to nonsteroidal anti-inflammatory drugs
        - **Late-onset non-eosinophilic:** no eosinophilia markers, no exhale nitric oxide markers; chronic or recurrent lower respiratory tract infections and gastroesophageal reflux disease
- **Inflammatory pathways:** A first step is to identify whether a patient has type 2 inflammation or non-type 2 inflammation; then identify whether they have elevated eosinophils, nitric oxide, or Immunoglobulin E (IgE). Eosinophils in the blood and sputum is known to correlate with the frequency of asthma exacerbations and the degree of airflow limitation.
    - **Type 2** pathway (prevalence 50% to 70% of all patients)
        - Cytokines interleukin-4, -5 and -13
        - Derived from Th2 cells, innate lymphoid cell type 2, or ILC2 cells, and mast cells
        - Attracts eosinophils from the bone marrow and allows them in the lung tissue
        - 300 to 400 eosinophils is the margin for type 2 inflammatory pathway

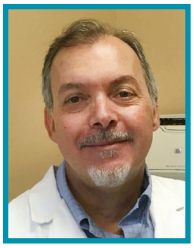
  - Variable levels of eosinophils in the sputum, airway tissue, and blood
  - Exhaled nitric oxide is a marker of type 2 pathway
  - Elevation of total IgE and specific IgE to a variety of different allergens (ie, dust mites, animal dander, mold)
- **Non-type 2** pathway (prevalence 30% to 40% of asthmatics)
  - IL-4, -5, and -13 are not involved in this pathway
  - IL-17 may be an important contributor to this pathway
  - Underlying related bronchial infection (not always)
  - Typically, no eosinophils; no increase in total or specific IgE
  - May have increased sputum neutrophils (>60% of the cell types in the induced sputum)
  - Non-allergic; allergy is not driving the disease

- A patient's **environment**, as well as their **adherence** to treatment, along with any **comorbidities** all play a role in the treatment strategy of asthma. **Allergen avoidance** is a key strategy to help patients with asthma minimize exacerbations. Clinicians need to consider the patient's environment: whether they are pet owners, or their specific working conditions, for example. An **assessment of adherence** to current and prior therapy is also required. Patient education is essential to communicate how a specific therapy works and the importance of proper use. Addressing and **managing comorbidities**, such as chronic rhinosinusitis, gastroesophageal reflux disease, vocal-cord dysfunction, and sleep apnea can also help address issues associated with asthma. Patients who have allergies often have IgE-mediated disease. Many patients who have chronic rhinosinusitis often have IL-5 or IL-4-mediated disease. Patients who have atopic dermatitis also often have IL-4-mediated disease.
- Identifying the type of disease helps the clinician select the most appropriate therapeutic strategy. A high-dose inhaled corticosteroid, along with a long-acting beta agonist in a single-combination inhaler, is standard therapy. If the therapy is not effective within a month or 2, adding a long-acting muscarinic receptor antagonist (LAMA) is often prescribed. For patients with severe asthma, if this course of treatment, taken for a period of 2 to 3 months, does not bring the patient's disease under control–and the patient is adherent to the therapy–then biologic medication should be considered. To determine which biologic agent, phenotyping will help with the selection process.
- Identifying the clinical **phenotype** helps facilitate a personalized approach to treatment based on the underlying asthma mechanism of inflammation. It allows the clinician to prescribe the right drug to the right patient at the right time. Phenotypes can also help determine which **endotype** is most likely to occur, thus helping to identify the most appropriate therapy. For example, if a patient has predominantly allergic asthma, an anti-IgE agent may be the best choice. If a patient has predominantly eosinophilic asthma, either anti-IL-5 or an anti-IL-4/13 therapy may be most appropriate. If a patient has an elevated nitric oxide level, an anti-IL-4/13 strategy is probably the most appropriate therapy.
- **Inflammatory biomarkers** are an additional measure to clinically differentiate asthmatics; biomarkers help identify which patients may be more severe and predict how well a patient may respond to therapies, identifying which strategies are useful for which patient. Biomarkers include cellular tests that measure eosinophils in the blood or sputum, or exhaled nitric oxide or IgE levels. The most severe type of asthma has been shown to have a combination of eosinophilia plus neutrophilia.
- **Biologics** are targeted therapies that identify specific mechanisms of action in given patients. These new agents may also help achieve disease modification or even disease remission. There are a variety of different biologic therapies currently available for the management of asthma. Anti-IL-5 therapies, including benralizumab, mepolizumab, and reslizumab, have all been shown to be effective in patients with eosinophilic asthma. Anti-IgE therapy, including omalizumab, has been shown to be effective in patients with allergic asthma. And the most recently approved, dupilumab, is anti-IL-4 receptor alpha therapy, which has been shown to improve lung function and reduce asthma exacerbations in patients with type 2 asthma, including both allergic asthma and eosinophilic asthma.
- If the patient is highly allergic, and has had asthma their entire life, with a history of food allergy, eczema, and/or allergic rhinitis, with elevated IgE, omalizumab may be the right choice. An anti-IL-5 or anti-IL-5Ra drug, such as mepolizumab, reslizumab, or benralizumab, may be more appropriate in a patient who has minimal allergy or later-onset disease, with an elevation of their blood eosinophil count. For patients who

do not have a high eosinophil count, but may have elevated exhaled nitric oxide, indicating they have a type 2 pathway, dupilumab, an IL-4/-13 receptor antagonist, recently approved, may be appropriate. Use of these biologics for patients with severe asthma has been shown to reduce exacerbations signifi cantly, as well as reduce the use of oral-corticosteroid requirements. Clinicians also need to consider the optimal treatment regimen based on the patient's asthma severity and comorbid conditions. In addition, it is important to consider the daily burden of disease and quality of life for the asthmatic patient.

By using these treatment strategies in the right patient at the right time, you can reduce exacerbations, reduce steroid dosing, and minimize side effects, to improve symptoms and asthma-related quality of life, including better sleep, better exercise, and better ability to stay and work effectively at their job. Selecting from the latest biologics treatment for individual patients, combined with allergen avoidance and allergy immunotherapy, is sure to have a significant impact on asthma management and benefits for your patients.

Yours sincerely,



Jonathan Corren, MD
Clinical Associate Professor of
Medicine and Pediatrics
Divisions of Clinical Immunology
and Allergy
David Geffen School of Medicine
at UCLA
Los Angeles, California

Michael E. Wechsler, MD
Professor of Medicine
Director, NJH Cohen
Family Asthma Institute
Department of Medicine
National Jewish Health
Denver, Colorado