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Management of Severe Asthma before Referral to the Severe Asthma Specialist

Tara F Carr, MD¹ and Monica Kraft, MD¹

¹Asthma and Airway Disease Research Center, University of Arizona, Tucson AZ

Abstract

Severe asthma is associated with significant morbidity and can be challenging to assess and control, due to heterogeneity of disease, complexity of diagnosis, and impact of comorbidities. A structured approach to the assessment and management of severe asthma may be helpful to the practicing clinician. First, it is important to confirm a diagnosis of asthma. In patients who are either not responding to treatment, or who require high doses of medication to control symptoms, it is highly possible that disease mimickers or comorbidities are present and can inhibit therapeutic responsiveness. The assessment and management of common comorbidities of asthma may dramatically impact disease control and thus medication requirement. Determining medication adherence and optimizing drug dose and delivery may separate out truly severe asthmatics from those not using medications regularly or properly. Next, while true personalized medicine for severe asthma is not yet realized, for those individuals with severe asthma, phenotypic characteristics of each patient may guide which therapeutic options may be most effective for that patient. Finally, evaluation and management of severe asthma at a referral center can add additional phenotyping, therapeutic, and diagnostic strategies.

Keywords

Biologic therapy; Comorbidities; Adherence; Inhaled corticosteroid; Phenotype; Severe asthma

Introduction

Asthma is heterogeneous, both in the clinical presentation and characteristics, or phenotype, and in terms of severity ¹. Management of asthma can be complex for providers and patients, particularly when the asthma is severe and/or difficult to control. This complexity is multifaceted: Challenges exist in asthma diagnosis, assessment, selection of therapy,

Corresponding Author: Tara F Carr, MD, 1501 N Campbell Ave, Tucson, AZ 85724-5030, Phone: 520-626-7514, Fax: 520-626-1876, tcarr@deptofmed.arizona.edu.

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confirmation of adherence, and evaluation of contributing comorbidities. Ideally, practitioners treating asthmatics will have access to a multidisciplinary team including nurses, respiratory therapists, psychologists/behavioral counselors and social workers, to optimize care from every aspect. Barriers to synthesizing and implementing asthma recommendations and best practices include, among others, insufficient knowledge of recommendations, lack of time and resources, and financial constraints to providing care². The purpose of this article is to discuss a practical, structured approach to assessment and management of severe asthma in a non-referral center. Therefore, most recommended testing is generally widely available, and the treatment discussion will focus on those clinically available and FDA-approved for asthma, or soon-to-be approved. This article is limited to a discussion of severe asthma in patients aged 6 to adult.

Overview of Asthma

Asthma is a chronic inflammatory disease of the airways. Individuals with asthma may describe a spectrum of symptoms, including recurrent wheezing, dyspnea, chest tightness, and cough. These symptoms reflect episodes of reversible airflow obstruction, which may remit spontaneously or with treatment. Over time, many patients with asthma experience progressive airway remodeling, leading to an incompletely reversible, or fixed, airflow obstruction. Further, inflammation in the asthmatic airway induces airway bronchial hyperresponsiveness to a variety of allergic, infectious, or irritant stimuli.

Asthma is a very common chronic disorder, and asthma prevalence is increasing with time³, perhaps due to better recognition and phenotyping. Asthma severity can range from intermittent to severe; more severe asthma is associated with significant morbidity and mortality. Severe asthma is a major cause of morbidity and health care costs, and affects 10% of all patients with asthma, i.e., approximately 2.5 million Americans. In the United States in 2013, 3630 individuals died from asthma, or nine people per day^{3, 4}. These data suggest asthma is often poorly controlled, despite the availability of pharmacologic therapies that are recommended in National and International Asthma Guidelines⁵⁻⁷.

Initial Approach to Severe Asthma in the Clinic

We recommend a structured approach to the assessment and management of severe asthma (Figure 1). First, it is important to confirm a diagnosis of asthma, using history, physical exam, and appropriate objective testing. For those patients with suspected severe asthma, as defined by requirement of high dose steroids for control or lack of control despite this therapy⁶, it is highly possible that disease mimickers or comorbidities are present which may inhibit therapeutic responsiveness. Therefore, important comorbidities of asthma should be thoroughly assessed and treated. Importantly, determining medication adherence and optimizing drug dose and delivery may differentiate severe asthmatic patients from those not using medications regularly or properly. For those with confirmed severe asthma, we recommend additional objective testing and phenotyping assessments, which may help to guide treatment. Finally, we present additional workup and interventions that would be considered within a referral center, some of which may be available for patient care outside a referral center.

1. Confirm Diagnosis of Asthma—Accurate diagnosis of asthma is important, as treatment will benefit both morbidity and mortality from this disorder. As many diseases have overlapping clinical findings with asthma, accuracy of clinical diagnosis is critical for planning appropriate treatment strategies, particularly in the setting of severe asthma. Two guidelines documents- the Global Strategy for Asthma Management and Prevention 2016 report update⁷ and the National Institutes of Health Guidelines for the Diagnosis and Management of Asthma Expert Panel Report-3 (EPR-3)⁵ provide recommendations for the diagnosis of asthma and a framework for the treatment of asthma. These guidelines emphasize evaluation of impairment and risk, with ongoing assessment of control. The severity of asthma as measured through these domains is then used to guide treatment. The European Respiratory Society and American Thoracic Society Task Force document on Severe Asthma⁶ provides guidance on issues specific to severe asthma, including diagnosis and evaluation.

The assessment and diagnosis of asthma starts with a comprehensive medical history and physical exam. Symptoms may include cough, wheeze, chest tightness, chest heaviness, and/or breathlessness. An asthma-based medical history should include documentation of symptom and exacerbation quality, frequency, and severity.

A thorough physical examination can be very helpful for determining characteristics and comorbidities of asthma. A chest x-ray should be performed in patients with new-onset or significantly changing respiratory symptoms, to rule out the presence of overt structural disease, malignancy, and infection.

Lung function testing can confirm airflow obstruction and measure reversibility or variability of airflow obstruction. Spirometry is a widely available, inexpensive, noninvasive test that measures dynamic pulmonary function: Expiratory and inspiratory flow rates and volumes. The ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) is used to diagnose airflow obstruction; a ratio value of less than the lower limit of normal, or less than 70% when the lower limit of normal is not available⁸, is consistent with obstructive disease. The forced mid expiratory flow between 25% and 75% (FEF₂₅₋₇₅) can be computed from the flow volume loop and correlates highly, though non linearly with FEV₁/FVC and can be more reflective of small airways obstruction than is FEV₁ or FEV₁/FVC^{9, 10}. FEF₂₅₋₇₅ may also be an early marker of small airways impairment¹¹, and reductions in this flow rate have been associated with asthma exacerbations, particularly in children¹².

In asthma, by definition, airflow obstruction (if present) should be at least partially reversible. This finding is helpful to distinguish asthma from other diseases of chronic irreversible airflow limitation, such as chronic bronchitis, emphysema, and bronchiectasis. Reversibility is less commonly seen in these diseases. Reversibility is measured by performing spirometry before and after treatment with an inhaled bronchodilator. Most protocols administer 4–8 puffs of albuterol sulfate (short acting beta-2 agonist, SABA) or ipratropium bromide, administered by hydrofluoroalkane (HFA) inhaler with spacer device. Reversibility is determined by an increase in FEV₁ of >200 mL and 12 percent from the baseline measure.

Per guidelines-based therapy, treatment should be initiated based on severity, and adjusted regularly to gain adequate disease control⁵. An individual with severe asthma should therefore be treated with a combination of high dose inhaled corticosteroid (ICS), equivalent to fluticasone propionate 500mcg daily ages 6–11, and 1000mcg daily ages 12 and up (Table 1), and additional controller such as a long acting beta agonist (LABA), to be used regularly for symptom control and prevention. Patients should also be prescribed a SABA for quick relief of symptoms. Importantly, providers need to teach patients how to correctly use their inhalers, distinguishing rescue from continuous-use treatments, and training patients in the proper technique to use each device. It should be noted that while high dose ICS is utilized for treatment of severe asthma, not all patients will receive a dose-dependent benefit from increasing doses of ICS. Benefits of high dose ICS should be balanced with long-term side effect profiles.

Medication non-adherence or poor inhaler technique can be identified in many patients with asthma, including those with severe asthma, and can impact asthma outcomes and quality of care, including risk of exacerbations in those with severe asthma^{13–15}. At each asthma assessment visit, it is imperative for the clinician to assess the continuity of use of controller medications as honestly as possible with patients, and to continually re-educate patients on the schedule, dosage, and technique for use of controller and rescue medications.

Medication non-adherence is often multifactorial. Some reasons for non-adherence may vary by patient demographic characteristics¹⁶. For example, medication adherence in older adults may be impacted by cognition or health literacy¹⁷. In school-aged children, medication adherence varies by parental education, socioeconomic status, gender, and ethnicity^{16, 18}. Cost of inhalers, lack of education or direction from the physician, and lack of disease understanding contribute to underuse of controller medications at all ages^{19,20}. Clinics can indirectly measure adherence through pharmacy records of medication fills and refills. Effective provider-patient communication is vital to understand the barriers to adherence in a given patient. Monitoring devices, electronic reminders and tracking tools, and ongoing educational interventions can be implemented to attempt to improve adherence, but these interventions are variably successful.

Finally, ineffective drug delivery to the lungs can preclude clinical benefit, further reducing interest in utilizing controllers regularly. Patient education on asthma inhaler use can improve asthma outcomes²¹. Assessing and correcting inhaler technique is important for all patients and should also be done at each visit¹⁹. Use of a spacer device may improve drug delivery for larger-particle therapies to the lung, particularly in patients with acute asthma symptoms, therefore prescription of a spacer is also recommended²².

2. Further Evaluate Suspected Severe Asthma and Comorbidities—Individuals with suspected severe asthma should undergo a careful systematic assessment to confirm this diagnosis, involving the techniques previously described, and to identify comorbidities or alternative diagnoses.

Environmental control can be crucially important to asthma management. Clinicians should question patients about known or suspected environmental triggers of asthma symptoms and

exacerbations. While the relationship between trigger avoidance and asthma control may seem obvious to clinicians, patients may underestimate exposures and under-perceive the impact of those exposures on disease control. Avoidance measures of these triggers, while not proven to alter disease course, may help improve overall control of asthma²³. Cigarette smoke exposure is one of the most common triggers of asthma symptoms and exacerbations²⁴. Smoking should be strongly discouraged for patients with asthma; importantly, avoidance of secondhand smoke is also required. Asthma pathogenesis and severity have been linked to various indoor allergens including mouse and rat urine, dust mite, cockroach, and pet dander. Furry pet allergen, particularly from the saliva, dander and other secretions of dogs and cats, is very small, easily transferred among locations, and is easily aerosolized. For individuals who are already sensitized to cat or dog antigen, minimizing exposure is encouraged to reduce the likelihood of developing asthma²⁵. In general, cleaning of the home, high efficiency air filters, and removal of the pet from commonly used areas (dog) or the building (cat) may be helpful to reduce burden of exposure. Mouse and rat antigens, particularly from urine, are aerosolized in small particles and thus can be easily inhaled into the lungs²⁶. Further, increasing amounts of antigen exposure correlates with increased risk of asthma development and higher degree of severity. This particularly affects inner-city children, where exposure can be markedly higher than children living in suburban or rural environments. Cockroaches also contribute to asthma pathogenesis and severity, disproportionately affecting residents of the inner-city²⁷. Control includes assessment and removal of exposure factors by patients and their family members; and if this is unsuccessful, may require professional extermination.

Dust mites are ubiquitous microscopic arachnids that thrive in humid environments. Mites feed on human and pet dander; allergens are mainly found in fecal pellets. Avoidance measures, such as tightly woven bedcovers, frequent washing of bedding, vacuuming walls and floors, and dehumidification may limit environmental dust mite burden²⁸. Outdoor and indoor molds have also been linked to asthma pathogenesis and severity^{29, 30}. Mold proteases and components are antigenic and can stimulate type-2 cellular inflammation³¹. Avoidance includes dehumidification and remediation of known indoor mold sources; recommendations to this end have recently been published^{32,33}.

For patients in whom environmental allergen exposures are suspected to contribute to asthma, testing for specific IgE antibodies against the antigen can easily confirm the presence of allergy. Testing may be performed as percutaneous and intradermal skin testing, or through serum assessment of antigen-specific IgE antibodies³⁴.

Allergic bronchopulmonary aspergillosis (ABPA) is a pronounced hypersensitivity reaction to molds, most commonly *Aspergillus fumigatus*, that develops in patients with asthma or cystic fibrosis. ABPA manifests with worsening clinical symptoms including breathlessness, wheezing, and cough productive of thick, often tan-colored, mucus plugs. ABPA is present in 10–39% of patients with severe asthma^{35–37}. This disease can progress to dramatic central bronchiectasis and end stage lung disease with fibrosis. In the appropriate clinical setting, ABPA is diagnosed with elevated IgE levels (greater than 417 IU/mL), positive skin testing or serum IgE to aspergillus, and aspergillus-specific IgE and IgG antibodies twice that expected for asthmatics³⁸. Peripheral eosinophilia, serum IgG precipitins to aspergillus

and radiographic infiltrates are commonly seen in ABPA. The mainstay of treatment is systemic steroids with gradual tapering to a clinical remission. Antifungal therapy and omalizumab can be used as adjunctive treatments, particularly for individuals who become steroid dependent or have frequent exacerbations of disease.

Bronchiectasis presents with chronic cough, mucus production, and recurrent respiratory infections³⁹. Bronchiectasis may develop as a result of recurrent infection (with or without immunodeficiency), ABPA, and rheumatologic disease. Patients with coexisting asthma and bronchiectasis have increased risk of asthma exacerbations, and therefore may be classified as having severe asthma. The diagnosis of bronchiectasis is made by cross-sectional lung imaging with high resolution CT scan; management focuses on airway clearance and control of infections; co-management with pulmonologists and infectious disease specialists may be helpful.

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases, most commonly cigarette smoke⁴⁰. Patients suffer from breathlessness, chronic cough, and sputum production, as well as history of risk factors for this disease. COPD is diagnosed by confirming post-bronchodilator airflow obstruction. With overlapping symptoms and similar pre-bronchodilator spirometric patterns, asthma may be mis-diagnosed as COPD; the reverse is also true. Significant inhalational exposure history and reduced pulmonary diffusion capacity can help to differentiate COPD from asthma. Complicating this distinction, asthma and COPD may coexist in the same patient, termed Asthma-COPD overlap syndrome⁴¹, and severe chronic asthma can lead to chronic airway remodeling and partially reversible obstruction. While guideline recommendations and prognosis differ between asthma and COPD, it is not yet clear how identifying the presence of coexisting asthma and COPD will change individual patient management.

Chronic rhinosinusitis (CRS) is defined as inflammation of one or more of the paranasal sinuses, for longer than 8–12 weeks, and presents as nasal congestion, drainage, and sinus opacification^{42, 43}. CRS affects up to 50% of patients with moderate to severe asthma, and is associated with more severe symptoms of asthma, and more frequent asthma exacerbations. Treatment of CRS with maximal medical therapy, at least three consecutive weeks of a broad-spectrum antibiotic and oral/intranasal corticosteroids, or surgical management via functional endoscopic sinus surgery, has been shown to improve asthma control⁴⁴. We assess for CRS in patients with symptoms of CRS, or those with cough as a prominent symptom of asthma, and treat aggressively with medical and surgical management as described in collaboration with otolaryngologists/rhinologists.

Symptomatic gastroesophageal reflux disease (GERD) is common in asthmatic patients, but the effect of treatment on asthma control or severity is currently unclear. GERD is thought to contribute to asthma through triggering increased vagal tone, vocal cord dysfunction, bronchial hyperreactivity, and possibly microaspiration. In the setting of reflux symptoms, a proton-pump inhibitor may reduce exacerbations and improve asthma symptoms^{45, 46}. However, this treatment has not been shown to be beneficial in uncontrolled asthmatics with

no evidence of reflux⁴⁷. For individuals with symptoms of GERD, including cough and chest discomfort, we treat with a trial of high dose proton pump inhibitors and/or h2 antagonists, and encourage lifestyle modifications including smaller meals, elevated head of bed, and avoiding evening snacks.

Vocal cord dysfunction (VCD) is caused by paroxysmal, inappropriate partial or complete closure of the vocal cords. Symptoms include recurrent spontaneous sudden episodes of breathlessness, often accompanied by hoarseness and stridor⁴⁸. Triggers of VCD include smoke, rhinitis, GERD and stress, which similarly can worsen asthma. VCD often coexists with asthma, but may mimic asthma and confound treatment leading to high healthcare utilization and costs⁴⁹. VCD can be suspected by symptoms, diagnosed by variable extrathoracic obstruction seen on spirometric flow-volume loops, or directly visualized via laryngoscopy. Treatment includes managing triggers and speech therapy.

Obesity, obstructive sleep apnea, and related psychological factors may contribute to asthma severity or perception^{6, 50}. Obese asthma may be a separate phenotype with unique pathobiological processes⁵¹. Deconditioning is present in many obese asthmatics; pulmonary rehabilitation programs are appropriate for individuals with severe asthma and reduced functional capacity from this disease⁵². Obstructive sleep apnea is correlated with severe asthma exacerbations⁵³. Asthma outcomes improve for patients with obstructive sleep apnea receiving treatment via continuous positive airway pressure⁵⁴. Continuous positive airway pressure may improve airway reactivity in asthmatics without obstructive sleep apnea, but has not been shown to improve asthma control⁵⁵. If available, pulmonary rehabilitation programs and treatment of obstructive sleep apnea can be important, nonpharmacologic tools for improving asthma control.

3. Confirm Severe Asthma

Definition of Severe Asthma: Assuming asthma diagnosis is accurate and comorbidities are being addressed, severe asthma is defined as asthma that requires treatment with guidelines-suggested medications such as high dose inhaled corticosteroids and a second controller for the previous year, and/or systemic corticosteroids for at least half of the previous year, to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy⁶. Uncontrolled asthma is defined as the presence at least one of the following characteristics: Persistently poor symptom control, two or more exacerbations requiring bursts of systemic corticosteroids in the preceding year, at least one serious exacerbation requiring hospitalization in the previous year, or chronic airflow limitation of FEV1<80% predicted with FEV1/FVC ratio less than the lower limit of normal⁶.

Further evaluation for severe asthma is recommended for those individuals regularly using high dose ICS/LABA with good technique, and particularly encouraged if a patient is achieving minimal or partial asthma control. These further tests can further confirm severe asthma, can rule out additional confounding diseases, and will provide biomarkers of the disease phenotype that may help guide next treatment options.

If not already done, high quality cross-sectional pulmonary imaging, with a high resolution, non-contrast chest CT scan, can be used to assess for comorbid or alternative diagnoses,

including emphysema, bronchiectasis, and fibrosis. Further lung function testing and pulmonary maneuvers can help to both rule out alternative diagnoses and phenotype severe asthma. Lung volumes measurements, through plethysmography, are utilized to rule out restrictive lung disease and will also demonstrate the presence of air trapping and/or hyperinflation. Measurements of diffusion capacity will evaluate the presence of emphysema or fibrosis.

Bronchoprovocation testing via methacholine inhalation may be utilized to measure the degree of airway hyperreactivity. This test is helpful for individuals with normal or near-normal lung function but for whom the diagnosis of severe asthma is suspected. Patients receive incrementally increasing exposures to the airway stimulant methacholine, and lung function is monitored after each dose. The exposure level that causes a 20% decrease in FEV1 is called the provocative concentration that causes a reduction of 20% in FEV1 (PC₂₀ FEV1). In the setting of methacholine challenge, a PC₂₀ FEV1 < 16 mg/ml is consistent with airways hyperresponsiveness which is characteristic of asthma.

Pharmacotherapy of Severe asthma: Adequate control of severe asthma, by definition, should prevent exacerbations and limit mortality due to asthma^{5,7}. A stepwise approach to therapy is recommended by national and international guidelines based on disease severity and each individual's response to therapy. This approach emphasizes use of controller medications. Doses are titrated to effect, or additional therapies are added as needed to achieve the necessary level of symptom control. At every level, assessment of proper inhaler device techniques, adherence to therapy, environmental control, and use of rescue inhalers for quick relief of sudden symptoms are recommended. Importantly, treatment should also identify and minimize medication side effects.

As previously discussed, inhaled corticosteroids with LABA are a mainstay of treatment for individuals with severe asthma. By definition, those individuals with severe asthma require high doses of corticosteroid to control disease, and often remain symptomatic despite this therapy. Interestingly, a subset of severe asthmatics is relatively corticosteroid insensitive, with relative or complete lack of clinical improvement from treatment with inhaled or systemic corticosteroids. Corticosteroid insensitivity may be more common in those with vitamin D deficiency or obesity. In contrast, eosinophilic or type-2 inflammation-high asthma may have a relative benefit from steroids when compared to those with non-eosinophilic, non-type-2 inflammation⁵⁶. Therefore, individuals with evidence of type-2 disease, such as peripheral blood eosinophils or elevated FeNO, are likely to show at least some benefit from corticosteroid treatment.

Beta-agonists confer smooth muscle relaxation and bronchodilation through beta-adrenergic receptors. The use of short and long acting beta-agonist medications in asthma has been a subject of concern surrounding evidence that these drugs may contribute to asthma treatment failure⁵⁷, particularly in individuals using LABA as monotherapy, or those with genetic differences in the beta-adrenergic receptor⁵⁸. However, recent results of United States Food and Drug Administration-mandated safety studies with combined inhaled corticosteroid-LABA therapy do not show evidence of adverse effects^{59, 60}. Multiple combination inhaled corticosteroid-LABA devices are available on the US market for treatment of asthma.

Choice of therapy may be largely driven by insurance coverage, which determines affordability of the drug. Patient preference may also impact compliance. Devices are available in hydrofluoroalkane (HFA) and dry powder inhaler mechanisms (Table 1). One dry powder inhaler (DPI) is approved for once daily use (fluticasone furoate-vilanterol), which may improve ease of use and adherence.

Leukotriene receptor antagonists or 5-lipoxygenase inhibitors may benefit severe asthmatics, particularly those with leukotriene-driven diseases such as aspirin exacerbated respiratory disease (AERD)⁶¹. Montelukast and zafirlukast both inhibit the type 1 cysteinyl leukotriene receptor, and are generally well tolerated with the exception of mood changes that may rarely occur in children or those with history of mood disorders⁶². Zileuton, which inhibits 5-lipoxygenase enzyme and thereby reduces cysteinyl leukotriene formation, can cause elevations in liver function tests and therefore monitoring of these parameters is recommended while patients are on this therapy. Patients with AERD may ultimately benefit most significantly from aspirin desensitization and long-term treatment with high dose aspirin to improve asthma and nasal polyposis control⁶³.

Long acting muscarinic antagonists (LAMA), such as tiotropium, can be beneficial as add-on therapy in severe asthma^{64, 65}. LAMAs inhibit the muscarinic acetylcholine receptor, with highest affinity for the M3 receptor, which is primarily responsible for regulation of airway mucus secretion and smooth muscle contraction⁶⁶. LAMAs have been shown in vitro and in animal models to have effects on airway inflammation, cellular responses, and airway remodeling⁶⁶. While it is not yet clear which patients with asthma will benefit from use of a LAMA, LAMAs have shown efficacy in treatment of non-eosinophilic asthma⁶⁷. Given the clinical benefit in COPD, there is the potential for use of LAMAs in asthma-COPD overlap syndrome⁶⁴, and may be of benefit for individuals with evidence of increased cholinergic tone such as slow resting pulse rate. LAMAs may function to reduce asthma exacerbations by inhibiting viral-induced molecular inflammation⁶⁸. LAMAs are generally well tolerated, with dry mouth as a common but non-limiting side effect. In our practice, because of the ease of use and relative availability of these drugs, we utilize LAMA as add-on therapy to ICS/LABA, or to high dose ICS (in patients not tolerating LABA) for a 1–2 month trial period. Tiotropium has been approved for treatment of asthma in patients 6 years old in the United States, and for adults in Europe.

Biological therapeutics, those with a specific pathobiological target, have been and continue to be developed for use in severe asthma with prespecified phenotypes or biomarkers. Three biologics are available currently in the United States for clinical use. Omalizumab is a monoclonal anti-IgE antibody that binds the constant region of the IgE heavy chain, thereby inhibiting binding of the molecule to its high affinity receptor. This medication is FDA approved for the treatment of moderate to severe persistent asthma, in patients with serum IgE levels between 30–700 IU/kL and evidence of aeroallergen sensitivity to a perennial allergen. Omalizumab can improve quality of life and symptom control scores, in addition to reducing exacerbations⁶⁹. Omalizumab may prevent or reduce the severity of viral-induced exacerbations^{70, 71}. Omalizumab is dosed based on serum IgE level and patient weight, and administered every 2–4 weeks subcutaneously in a monitored setting. Risks of omalizumab include anaphylaxis, and the potential for cardiovascular or cerebrovascular events, and

potential risk of cancer^{72, 73}. Our practice is to use this medication for a 4–6 month trial to assess benefit in patients with exposure to a clinically relevant allergen.

Mepolizumab and Reslizumab are monoclonal antibodies against IL-5 that are FDA approved for the treatment of severe eosinophilic asthma. Mepolizumab is administered once monthly as a subcutaneous injection. Reslizumab is an IV formulation that is administered once monthly⁷⁴. These medications have been shown to reduce asthma exacerbations in those with severe eosinophilic asthma^{75, 76}. Anti-IL-5 treatment has been shown to be particularly efficacious in patients who demonstrate high sputum (> 3%) or blood eosinophils (> 300/ μ l), but is approved for use in those with blood eosinophil absolute counts of > 150/ μ l.^{77–80} We prescribe these medications for patients with marked eosinophilia >300/ μ l, for those with eosinophilia without significant atopy, and for those who have previously failed omalizumab.

4. Evaluation and Phenotyping at a Referral Center

Additional Evaluation at a Referral Center: A referral center often has access to multidisciplinary care teams and specialized testing that can further evaluate severe asthma. For example, methacholine challenge testing can be performed with a concurrent laryngoscopy to assess for the contribution of vocal cord dysfunction to symptoms. Exercise pulmonary function testing can be performed in athletes with exercise-induced symptoms to evaluate for vocal cord dysfunction or exercise-induced bronchospasm. Cardiopulmonary exercise testing can identify non-asthma contributing factors to dyspnea⁸¹.

If patients have symptoms concerning for GERD, but show incomplete benefit with high dose medical therapy and lifestyle changes, an esophageal pH probe with manometry and impedance testing can help to define the extent of esophageal dysfunction and GERD and are performed by gastroenterologists or gastrointestinal surgeons. Surgical therapy of GERD may help reduce symptoms in patients with asthma however its effect on severe asthma remains unclear⁸². Our center utilizes a minimally invasive surgical team approach and has observed reduced steroid requirement post-fundoplication in individuals with severe asthma and medically refractory GERD.

Specimens from the lower airway will provide phenotypic information and assessment of comorbidities. Sputum for cell counts and culture may be spontaneously provided, or induction can be performed. Bronchoscopy will obtain cells, specimen for bacterial and fungal cultures, and allow for inspection of the airway. Biopsy, through transbronchial or open lung approaches, may be necessary for refractory asthmatics to rule out comorbid structural lung diseases⁸³.

Phenotyping Severe Asthma: The heterogeneity of pathobiological processes underlying asthma contributes to the inter-individual variability in response to asthma treatments^{84, 85}. Severe asthma is a highly heterogeneous condition. Therefore, optimizing treatment for each individual with severe asthma will require the detection of asthma subphenotypes and endotypes, and the underlying molecular mechanisms responsible for those traits. These subgroups, in turn, are expected to respond differentially to biologic therapies in severe asthma. The current state of the art and practice for treatment of severe asthma is not quite at

the level of precision medicine. However, clues to treatment efficacy have been uncovered through understanding of the different molecular pathways of asthma.

An initial, relatively successful approach to phenotyping was to distinguish phenotypes based on T helper 2 (Th2) or type 2 (T2)-related biomarkers such as FeNO, sputum/blood eosinophils⁸⁶ and Th2 or T2 -high or T2 low gene expression (IL-4, IL-5, IL-13) in the airway epithelium or in sputum. Increased expression of these biomarkers has been associated with better responses to corticosteroids⁸⁶. Therefore, many severe asthma experts identify patients with elevated blood and sputum eosinophil levels as likely to benefit from corticosteroids. However, many severe asthma patients have a persistent T2 phenotypic profile including peripheral and airway eosinophilia despite intense corticosteroid treatment and therefore this therapy is not curative. Type 2 innate lymphoid cells residing in the airway are also sources of interleukin IL-5 and IL-13⁸⁷, may constitute alternative pathways for the production of these cytokines, and may be prominent pathways in even non-atopic disease. Biologics inhibiting each of these cytokines have been developed, but it remains unclear which severe asthma patient will respond to which therapy, because reliable biomarkers have not yet been fully developed.

Less is known about the mechanisms underlying the non-T2 asthma phenotype. These patients have a neutrophilic sputum cellular predominance, but some had paucigranulocytic sputum⁸⁸. Th17 cells are CD4+ T cells that express IL-17 family cytokines and mediate neutrophil activation through the production of IL-8. Th17 cytokines cells have been localized in the airways of patients with severe asthma⁸⁹, and may mediate corticosteroid-resistant airway inflammation⁹⁰. Therefore, the IL-17 pathways may be targets of disease control in severe asthma. Further, chronic infection with atypical bacteria may contribute to severe asthma in a subset of patients, in whom macrolide antibiotics could provide therapeutic benefit⁹¹.

Acknowledging the imperfect phenotyping strategies currently available, we routinely test serum IgE and blood eosinophils in our severe asthma patients. These tests are widely available, reproducible, and provide us some guidance toward potentially beneficial drug therapies as described. Additional phenotyping measurements which may help guide management strategies include steroid-evoked phenotyping, nitric oxide measurement, and assessment of small airways disease. Steroid-evoked phenotyping includes assessing clinical and functional improvement in asthma after administration of systemic corticosteroids, such as intramuscular triamcinolone acetonide⁹². This can identify individuals who are steroid-unresponsive, and can indirectly identify those who may be non-adherent with their prescribed corticosteroid therapies. For example, those with significant reduction in peripheral eosinophils or symptomatic improvement after intramuscular steroids might not be taking their high dose inhaled or systemic corticosteroids as prescribed.

Nitric oxide is a widely distributed endogenous regulatory molecule synthesized by a family of enzymes, the nitric oxide synthases. Inducible nitric oxide synthase-derived nitric oxide is predominantly produced in airway epithelial cells throughout the lung and increase in asthma during type-2 driven, eosinophilic inflammation. Measurement of fractional exhaled nitric oxide (FeNO) from the lung, if available, is therefore considered to be a potentially

useful non-invasive biomarker reflecting eosinophilic airway inflammation. Impulse oscillometry, an effort independent measurement of small airway function, requires only passive cooperation from the patient⁹³ to measure pulmonary impedance and other pressures. These measurements can identify obstruction of small airways^{94, 95}, and the related characteristics of asthma control, severity⁹⁶ and response to oral bronchodilators⁹⁷.

The degree of small airways obstruction in severe asthma may be a useful phenotypic marker, as spirometric determination of small airways dysfunction has been shown to correlate with clinical asthma outcomes⁹⁸. For example, in SARP, individuals with more severe dysfunction of small airways, measured by reduction in spirometric measurement of FEF₂₅₋₇₅, had more frequent asthma symptoms and higher healthcare utilization, and were characterized by higher FeNO, IgE levels, and bronchial hyperreactivity⁹⁹. Small airways dysfunction or air trapping is also positively correlated with increased symptoms¹⁰⁰, exacerbation frequency in both adults and children with exacerbation-prone asthma¹⁰¹, and with systemic steroid use¹².

Notably, drug distribution may contribute to success of topically inhaled medications, particularly in the setting of severe asthma with small airways disease. Pulmonary distribution of medication is impacted by the size of the inhaled particle, measured in mass mean aerodynamic diameter (MMAD). Smaller particles, those with MMAD of <2 microns delivered via MDI, have been shown to deliver drug more effectively to the lower airways, conferring clinical benefit at lower doses than with large particle sizes^{102, 103}. As prescribing inhalers with different particle sizes may impact an individual's response to inhaler treatment, this may be taken into consideration when prescribing therapy for severe asthma (Table 1).

Finally, this is an exciting time for the treatment of severe asthma, given the recent advances in phenotyping and endotyping. We anticipate ongoing work to improve the application of precision treatments to patients with asthma. Referral centers may have access to novel asthma therapeutic interventions, or medications, through participation in investigator-initiated or industry-sponsored clinical trials. Biologic therapies directed at T2 and non-T2 mechanisms are in varying stages of development for asthma. Finally, there remains the potential for existing small molecule medications or non-T2 biologics to be repurposed for severe asthma.

Conclusions

Diagnosis and management of severe asthma can be challenging. However, using a structured assessment and management plan may reduce the likelihood of misdiagnosis of severe asthma, may assist in the recognition and treatment of common comorbid diseases, and can help providers identify therapeutic strategies likely to show benefit for severe asthma.

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Abbreviations

AERD	Aspirin-exacerbated respiratory disease
FeNO	Fractional exhaled nitric oxide
FEF₂₅₋₇₅	Forced mid expiratory flow between 25% and 75%
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastro-esophageal reflux
HFA	Hydrofluoroalkane
Ig	Immunoglobulin
IL	Interleukin
LABA	Long acting beta-2 agonist
MMAD	Mass mean aerodynamic diameter
MDI	Metered-dose inhaler
SARP	Severe Asthma Research Program
VCD	Vocal cord dysfunction

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Is this asthma?	Confirm Asthma Diagnosis History/Physical Spirometry with reversibility and chest x-ray Address medication adherence, technique
What is contributing to the asthma?	Further Evaluate Suspected Severe Asthma Assess and manage comorbidities Atopy, Allergic Bronchopulmonary aspergillosis, chronic sinusitis, chronic obstructive pulmonary disease, gastro-esophageal reflux disease, vocal cord dysfunction, obstructive sleep apnea, obesity, depression
Is this severe asthma?	Confirm Severe Asthma Plethysmography, DLCO Methacholine challenge, FeNO if available Biomarkers: Blood eosinophils, IgE Imaging: High resolution CT scan of lungs Treatment options beyond guidelines
What would a referral center add?	Additional workup for phenotyping, comorbidities Additional Therapeutics Small particle devices Novel investigational interventions

Figure 1.

Approach to assessing and managing severe asthma in the clinical setting.

Table 1

Comparative high ICS dosages and preparations for children 5–11 years and for adults (>12 years)

DRUG (dose per actuation)	High dose, in ug		Combination	
	6–12 yrs	>12 yrs	LABA, if available	MMAD (μ -M)
Beclomethasone dipropionate (HFA) (40, 80 mcg)	320	1000	--	1.1
Budesonide (DPI) (90, 180 mcg)	800	1600	Formoterol (HFA)	3.7
Budesonide (nebulized) (500 mcg)	1000	1000	--	2.9
Ciclesonide (HFA) (80, 160 mcg)	160	320	--	1.1
Flunisolide (HFA) (80 mcg)	160	320	--	1.2
Fluticasone furoate (DPI) (100, 200 mcg)	200	200	Vilanterol (DPI)	4.0
Fluticasone propionate (DPI) (50, 100, 250 mcg)	500	1000	Salmeterol (DPI and HFA)	5.4
(HFA) (44, 110, 220 mcg)				2.4–3.2
Mometasone furoate (DPI) (110, 220 mcg)	500	800	Formoterol (HFA)	2.2
(HFA)(100,200 mcg)				3.7

DPI, dry powder inhaler; MDI, metered-dose inhaler; HFA, hydrofluoroalkane; MMAD, mass mean aerodynamic diameter; na, not available

* MMAD for ICS alone; may be different in combination ICS/LABA preparations