

Severe Asthma: What Makes It So Hard to Manage?

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Severe asthma presents significant management challenges. Patients can be difficult to control despite use of current standard-of-care therapy, including inhaled corticosteroids and long-acting β -agonists. Alternative diagnoses, noncompliance, and comorbidities all can influence asthma control, future risk, and response to currently available therapy. Definitions of severe asthma evaluate and address these confounding variables, and yet patients are still symptomatic despite aggressive, appropriate therapy. Severe asthma has a distinct pathophysiology including airway remodeling that contributes to the decreased effectiveness of standard therapy. Multiple phenotypes exist within severe asthma that likely require distinct therapeutic approaches to achieve control and improve long-term health outcomes. New therapeutic approaches to these distinct phenotypes will improve our understanding and treatment of this difficult-to-manage disease.

Introduction

Most patients with asthma have mild to moderate disease that can be controlled with inhaled corticosteroids (ICS) combined with bronchodilators for relief of symptoms. Unfortunately, a subset of patients with asthma cannot achieve adequate control of their symptoms despite appropriate treatment that includes high-dose inhaled corticosteroids. This heterogeneous group of patients, who have what is known as severe persistent asthma (SA), present a distinct challenge to clinicians, who struggle to best manage their disease while limiting side effects. The mechanisms that make these patients so hard to manage are complex, multifactorial, and incompletely understood. For this reason, national guidelines directing clinicians on how to treat SA are incomplete, and clinicians are often

left wondering how to proceed with viable options. In this review, we address the difficulties and challenges of dealing with SA as well as new approaches to the management and treatment of these patients.

Defining Severe Persistent Asthma

Overall, 5% to 15% of asthma patients are considered to have SA depending on how it is defined. The first clinical challenge is to agree on a definition of SA that encompasses this very heterogeneous group. Multiple attempts have been made to characterize and define SA, but a universally adopted definition has been elusive (Table 1) [1–5]. Across these various definitions, criteria generally require a dependence on high-dose ICS treatment and increased health care utilization due to lack of control [6•]. For example, using the American Thoracic Society definition, for patients to be classified as having SA, they must have depended on high-dose ICS (≥ 880 μg of fluticasone or equivalent daily) or oral corticosteroids (OCS) for more than 50% of the preceding year [2]. This description of SA should correctly identify patients who are still symptomatic despite receiving the highest levels of treatment, who are most exposed to potential side effects of aggressive treatment, and who are using a disproportionate amount of health resources.

SA cannot be easily identified after just one clinical evaluation. Pretreatment classification of asthma severity does not predict future control. Clinical features that may be more characteristic of SA (eg, adult onset, aspirin sensitivity, nonatopy, female predominance) do not have sufficient predictive value. Although SA patients generally have lower lung function, no physiologic parameter by itself can adequately define this condition. Measurable biomarkers and potential genetic links that distinguish mild asthma from SA have been reported but have not been clinically validated in well-defined cohorts of SA. Without any available biomarker, genetic test, or physiologic test to identify SA, a prolonged temporal relationship with repeated attempts at treatment titration, assurance of treatment compliance, and exclusion of alternative diagnosis is necessary before determining if a patient fulfills the criteria for SA.

A patient with asthma not adequately controlled on standard treatment does not automatically have SA. The Gaining Optimal Asthma Control study proved that control can be achieved in most previously uncontrolled patients if treatment guideline recommendations are strictly fol-

Table 1. Definitions and characterizations of severe asthma

Study	Year	Definition of severe asthma
European Respiratory Society Task Force on Difficult/Therapy-Resistant Asthma	1999	Poorly controlled in terms of chronic symptoms, episodic exacerbations, persistent and variable airway obstruction, and continued requirement for short-acting β -agonists despite delivery of a reasonable amount of inhaled corticosteroids
American Thoracic Society workshop on refractory asthma	2000	Persistent symptoms, exacerbations, or airway obstruction despite high medication use, or patients who require high medication use to maintain good control
ENFUMOSA	2003	1 or more exacerbations in the previous year despite use of oral or high-dose inhaled corticosteroids
TENOR study	2003	High use of health care systems or medications in the past year
Severe Asthma Research Program	2007	Used American Thoracic Society workshop definition
ENFUMOSA—European Network for Understanding Mechanisms of Severe Asthma; TENOR—The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens.		

lowed [7]. These results suggest that many asthmatics with uncontrolled symptoms just require more aggressive treatment and should not be considered as having SA based on symptoms alone. However, the Gaining Optimal Asthma Control study also reported that 38% of patients with asthma could not achieve control even after an increasing titration of ICS to high doses over 1 year [7]. Although some of these patients could have been considered as having SA, they would not meet criteria for SA until they were evaluated for difficult-to-control asthma.

Difficult-to-Control Asthma

Many patients thought to suffer from SA can be better classified initially as having difficult-to-control asthma. Difficult-to-control asthma describes patients with persistent asthma symptoms despite aggressive therapy who have not been appropriately evaluated for noncompliance, alternative diagnosis, or comorbidities. It can be helpful to think of genuine SA as that which requires—and not just necessarily is prescribed—high-intensity treatment [6•]. In these terms, patients who are unintentionally overtreated will not be erroneously labeled as having SA. Difficult-to-control asthma also can be thought of as potentially treatment responsive if other modifiable confounders can be ameliorated. Making the distinction between SA and difficult-to-control asthma can be complex and requires a thorough and aggressive work-up. It often requires the assistance of specialized asthma centers to systemically review alternative diagnoses, aggressively rule out the confounding factors, and confirm adherence [8,9]. A systematic evaluation of patients referred to specialized centers for asthma identified that 30% to 50% of these patients are actually just difficult to control [8,9].

Alternative Diagnosis

The rate of misdiagnosis of nonasthmatic conditions as SA has been reported to be as high as 12% [9]. In addition,

about one third of difficult-to-control asthma cases have been shown to have other or additional diagnoses responsible for the respiratory symptoms [8,9]. Accordingly, a careful review of the differential diagnosis of asthma needs to be performed before labeling someone as having SA (Table 2).

Compliance

Nonadherence to treatment is always a consideration when standard therapy does not provide adequate control. Patients who are not fully compliant should not be diagnosed with SA, but practically speaking, detecting poor compliance is a significant challenge in the clinical setting and at times is difficult to rule out. Detecting serum prednisolone and suppression of serum cortisol levels can be used to confirm compliance with OCS use, but methods of measuring ICS compliance, such as canister weight or pressure-actuated/electronic counters, have not been widely adopted in clinical practice. Although the criteria for SA usually require compliance to be confirmed, this may be unattainable in clinical practice. There is evidence that difficult-to-control asthma patients are less compliant than non-SA patients, as studies have shown that noncompliance rates can be as high as 32% to 56% [8–10]. If noncompliance is present, it is not clear if this leads to the development of SA or if noncompliance arises due to patient perceived or actual ineffectiveness of standard treatment. No interventions have been reported to improve patient compliance in difficult-to-control asthma or SA.

Comorbidities

Most patients with SA have comorbidities that may make their symptoms more difficult to manage. These comorbidities could lead to perceived poor control by affecting airway function or by directly causing respiratory symptoms independent of asthma. Unfortunately, treatment of comorbidities in SA has not convincingly led to improved control [8,9].

Table 2. Differential diagnosis of severe asthma

Congestive heart failure
Upper airway obstruction
Vocal cord dysfunction
Dysfunctional breathlessness
Chronic obstructive pulmonary disease
Cystic fibrosis
Bronchiectasis
Bronchiolitis obliterans
Allergic bronchopulmonary aspergillosis
Hypersensitivity pneumonitis
Churg-Strauss syndrome
Eosinophilic pneumonia

Obesity

A relationship between SA and obesity exists, but the details are still being elucidated. Increasing body mass index and obesity have been shown to correlate with more SA, particularly in women [1,11–13]. SA patients in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort who gained weight independent of OCS use were found to have worse asthma-related health outcomes [14]. On the other hand, SA patients in the Severe Asthma Research Program did not have an increased incidence of obesity [5]. There has been speculation that the increased adipose tissue in obese individuals creates a heightened systemic inflammatory response that has negative effects on asthma control. However, in a study comparing obese and nonobese therapy-resistant patients with asthma, obese patients actually had improved airflow and decreased markers of airway inflammation [15•]. As expected, obese patients had decreased lung volumes and an increased risk for gastroesophageal reflux disease (GERD) and obstructive sleep apnea [15•]. These observations suggest that obese patients with SA have less severe airway inflammation but greater altered lung volumes and incidence of comorbid factors. Weight reduction may improve asthma control in obese patients with SA by reducing the impact of comorbid factors and attenuating the negative effects on lung volumes. Accordingly, weight loss has been reported to improve lung volumes in non-SA patients but with less pronounced effects on airway obstruction and reactivity [16,17]. There is also evidence indicating relative steroid unresponsiveness in obese patients, with elevated body mass index being associated with a blunted in vitro response to steroids [18]. Based on this information, the management approach in patients with SA who are obese should focus on weight reduction and adequate control of comorbid factors rather than intensifying anti-inflammatory therapy.

Smoking

It is not clear if smoking plays a role in the development or persistence of SA. Smoking has never been identified as

an independent risk factor for SA, but significant smoking history is often an exclusion criterion in asthma studies. There is also general speculation that individuals with more severe asthma symptoms would be less likely to become or remain regular smokers. The few SA patients who were smokers in the TENOR study had an increased risk for the development of persistent airflow obstruction [19•]. Treatment for SA patients who are active smokers should focus on tobacco cessation, as this has been shown to improve lung function and decrease markers of airway inflammation in non-SA patients [20]. Smoking seems to impair the efficacy of corticosteroid treatment, and avoidance may at least partially restore corticosteroid responsiveness in mild asthma [21–23]. Beyond these observations, there have been no dedicated studies in smokers with SA to better determine the role smoking plays in these patients or the optimal treatment regimen.

Psychiatric illness

Conflicting evidence exists on how psychiatric illnesses are linked to SA. It has been reported that severe forms of psychiatric illnesses are not associated with SA [24]. However, studies of difficult-to-control asthma have reported rates of major psychopathology ranging from 10% to 49% [8,9]. In addition, patients who have suffered from near-fatal or brittle asthma have high lifetime prevalence of psychiatric symptoms and morbidity [25,26]. However, another study could not differentiate between life-threatening attacks and admissions for less severe asthma exacerbations based on psychological factors [27]. It also has been proposed that some of the increased health care utilization for SA can be explained by coexisting psychopathology [28]. Longitudinal studies to clarify whether psychosocial disturbances are the cause or consequence of SA are lacking. In addition, there is no evidence to indicate that treatment of psychological disorders can improve control in SA [8,9,29].

Gastroesophageal reflux disease and rhinitis

GERD and rhinitis are exceedingly common in SA [5,8,30,31]. Moderate to severe rhinitis has been reported to be a predictor of uncontrolled asthma [32]. Although a causal association between these common comorbidities and difficult-to-control asthma is tantalizing and plausible, it has not been proven. There is conflicting evidence regarding whether treating GERD and rhinitis in milder forms of asthma can lead to improved control [8,9,30], but consensus standard-of-care recommendations indicate that they should be treated aggressively if present. SA with concurrent rhinitis should be treated with intranasal corticosteroids. Patients with SA with symptomatic GERD should be treated with an empiric trial of a twice-daily proton pump inhibitor to be taken before meals and should be instructed on GERD lifestyle changes. Objective measures of response should be sought to determine effectiveness. Treatment of asymptomatic GERD in uncontrolled asthma is not recommended [33].

Table 3. Proposed phenotypes of severe asthma

Early-onset
Late-onset
Eosinophilic
Noneosinophilic neutrophilic
Noneosinophilic paucigranulocytic
Intrinsic
Extrinsic
Brittle
Near-fatal
Stable airflow limitation
Aspirin-sensitive
Corticosteroid-resistant
Atopic with elevated IgE
Fungal sensitization

Disease Heterogeneity

SA is not homogeneous and is likely made up of multiple known and yet-undefined phenotypes. Many attempts have been made to better characterize asthma phenotypes using clinical, physiologic, exacerbating, and pathobiologic features (Table 3). These phenotypes are unlikely to be mutually exclusive or static, and a patient may display characteristics of several phenotypes at the same time or over time. Unfortunately, there is no current standard method of how to best define SA phenotypes. A validated classification system that incorporates the complexity of different asthma phenotypes and has the ability to predict responses to specific management strategies is needed. Novel techniques, such as cluster analysis, have been used to identify subgroups of asthma, with two subgroups described that exhibited marked discordance between symptoms and airway inflammation that were specific to refractory asthma [34•]. Importantly, an inflammation-guided treatment strategy in these patients led to a decreased exacerbation frequency in the inflammation-predominant cluster while at the same time avoiding overtreatment in the symptom-predominant cluster [34•]. A method of practically identifying a predominant phenotype has not been established. For example, whether inflammatory subtypes can be reliably and consistently distinguished by sputum analysis and to what extent they represent stable airway pathology is not known [35]. This inability to characterize and identify these subgroups likely plays a pivotal role in making SA so difficult to manage. Identification of these distinct phenotypes with specific biomarkers will likely lead to improved and distinct management strategies.

Corticosteroid Insensitivity

A well-defined phenotype in SA relates to patient response to corticosteroid treatment. Complete corticosteroid resistance in SA is likely rare. Most SA patients are better

thought of as corticosteroid dependent or less responsive to corticosteroids, as many receive some type of benefit. This is demonstrated by deterioration in control seen with cessation of corticosteroid therapy. An essential aspect of managing all SA patients is balancing the benefits and risks of systemic and high-dose corticosteroid use. It is critically important to have the ability to know if and when a patient should increase, decrease, or discontinue his or her corticosteroid dose.

Persistent eosinophilic airway inflammation that is seemingly resistant to ICS is a described SA phenotype [1,36–38]. Persistent eosinophilia in the face of intensive anti-inflammatory treatment most likely represents a shift in the dose-responsive curve rather than true resistance to corticosteroids. Supporting this theory is a study of SA patients with persistent sputum eosinophilia despite use of high-dose ICS and/or OCS who normalized their sputum eosinophils and decreased their rescue medication score after treatment with high-dose intramuscular corticosteroids [39]. These data would suggest that SA patients with persistent eosinophilia require a trial of higher doses of ICS. Accordingly, it has been suggested that this persistent eosinophilic phenotype may be more of an indication of disease activity than a fixed disease [39].

As this eosinophilic phenotype may remain corticosteroid responsive, albeit at higher doses, novel mechanisms to reduce corticosteroid side effects are being developed. Ciclesonide, an ICS that is only converted to active drug in the airway, has been shown to maintain control while reducing OCS dose in patients with previous corticosteroid-dependent SA [40]. Whether ciclesonide will result in less corticosteroid-induced adverse events is not clear, but this potential result is suggested by its diminished hypothalamic-pituitary-adrenal axis suppression [40,41]. Investigation into inhalation delivery of monodispersed particles that can lead to more precise distal delivery of ICS may be beneficial [42]. Lastly, dissociated corticosteroids that do not activate the mechanisms that lead to side effects but preserve therapeutic anti-inflammatory effects are being investigated [41].

More precise titration of corticosteroids in SA patients with eosinophilic inflammation using biomarkers has been shown to be beneficial. In a heterogeneous group of asthmatics, most of whom had SA, adjusting corticosteroid therapy using sputum eosinophil counts rather than standard management led to a decrease in hyperresponsiveness, severe exacerbations, and OCS use, with no difference in total ICS or OCS use [43]. Although fractional excretion of nitric oxide (FE_{NO}) measurements can identify SA patients treated with corticosteroids who have persistent airway eosinophilia, use of FE_{NO} to guide management has not been investigated in SA patients [44]. More distal alveolar nitric oxide measurements may also prove to be a useful biomarker given the importance of small airway inflammation in some patients with SA [45,46].

At the same time, it is important to identify patients who may not benefit from prolonged corticosteroid exposure. SA patients often take very high doses of ICS (> 2000 µg/d) with-

out data to support this approach. Patients in the TENOR study actually had better control on low-dose ICS/long-acting β -agonists (LABAs) than those on high-dose ICS/LABAs or no combination therapy at all [47•]. The implications of this observation are that incremental dose increases above the low-dose ICS/LABAs may not provide added clinical benefit in certain SA patients [47•]. In addition, non-SA patients with noneosinophilic inflammation have been reported to respond less to ICS [48–50]. In these patients who are stable, it is suggested that ICS can be successfully titrated down [51]. Whether these data can be extrapolated to SA is not known but needs to be investigated.

Distinct Pathophysiology

Most SA does not just seem to represent a continuum of a milder form of asthma but rather appears to have unique physiologic features. The typical physiologic parameters that define asthma, such as forced expiratory volume in 1 second (FEV_1) and airway reactivity, cannot completely explain SA. Correlation between FEV_1 and disease symptoms is poor, and some SA phenotypes can have normal FEV_1 between exacerbation episodes [52,53]. Airway hyperreactivity also has only a weak relationship with severity and symptoms [54,55]. Other characteristics of airway hyperreactivity, such as the rapidity of lung function change with irritant exposure, may better explain some components of SA [56,57].

As these typical physiologic components of asthma cannot completely explain SA, it is possible that other measurable physiologic features are more closely linked to severity. Increased lung collapsibility may be an important characteristic of SA. Reduced elastic recoil, possibly due to small airway–parenchyma uncoupling, has been reported to be a risk factor for fatal asthma [58–60]. Increased airway collapse and enhanced airway closure also have been described in SA [36,61]. How to best manage patients with these physiologic abnormalities is not known.

Although persistent airway obstruction is not a universal requirement for SA, it is a common physiologic feature [19•,38,62]. The particularly concerning aspect of this feature of SA is its continued progression while on aggressive standard therapy [38,62]. The exact mechanism of progressive airflow obstruction is not known but could be due in part to persistent airway inflammation [38,62,63]. This is suggested by the strong associations of persistent airway obstruction with elevated sputum, blood, and airway eosinophilia; FE_{NO} ; and periods of instability [37,38,62]. Elevated FE_{NO} also has been shown to predict accelerated decline in airflow in SA, particularly if the patient has normal lung function [45]. Current therapies do not appear to reverse this persistent airflow limitation in SA.

Need for Targeted Therapy

Although current asthma guidelines acknowledge that complete control of asthma may not always be possible,

alternative management strategies for SA are limited. Beyond omalizumab, which is the only add-on step 4 therapy with category A evidence in the updated 2008 Global Initiative for Asthma, no convincing clinical trials have determined what the next best treatment option should be after oral corticosteroids. SA patients represent some of the most challenging patients for whom to care, as they are found at the limits of what published treatment guidelines can offer. SA patients often have a compromised level of control, frequent use of rescue medication, and a degree of chronic lung function impairment that needs to be accepted to avoid exposure to futile treatments and potential side effects of medications.

Given the limited options for successfully treating SA, further investigation into targeted therapy is needed. It seems critical to better delineate phenotypes of SA that may share the same asthma syndrome but differ in their mechanism of disease and response to treatment. With better identification of these subgroups, future studies could be designed with specifically refined entry criteria and subgroup analysis so as to not discard potentially beneficial treatments. It will be important for future studies to choose the correct patient population, with attempts to exclude difficult-to-control asthmatics and only include genuine SA with the desired specific phenotype and outcome measure identified.

Omalizumab for atopic SA patients with an elevated IgE level has been shown to be an effective add-on therapy [64,65]. In patients with strictly defined SA with inadequately controlled symptoms and frequent exacerbations despite Global Initiative for Asthma step 4 treatment, omalizumab significantly reduced the rate of clinically significant exacerbations and emergency department visits [64,65]. It should be considered standard of care in this specific phenotype. Whether other patients, such as those with IgE levels outside the approved range, can benefit is a consideration for future trials.

Another atopic group that may benefit from specific add-on therapy is that of SA patients with fungal sensitization. Specific fungal sensitization in the general population appears to be uncommon but may be over-represented in SA patients [66]. This entity is difficult to define clinically given the major disconnect between skin and radioallergosorbent testing and the use of imprecise, manufacturer-dependent fungi allergy testing reagents [66]. One study recently did show that most of these patients achieved improvement in quality-of-life scores after treatment with itraconazole [67]. Further investigations are needed to clarify the characteristics of this phenotype and mechanism of action of the antifungal.

Aspirin-sensitive pathophysiology suggests that drugs that modify the leukotriene pathway may be helpful in SA. As such, targeted therapy with leukotriene modifiers and 5-lipoxygenase inhibitors have consistently shown benefit in aspirin-sensitive asthmatics [68,69]. Although no studies have systemically evaluated the response of aspirin-sensitive SA patients

to leukotriene antagonists, the low side effect profile should warrant a trial in this phenotype.

Targeting the T-helper type 2 cytokines with antibodies against interleukin (IL)-4, IL-5, and IL-13 may also hold promise given their relationship with eosinophils and key role in chronic inflammation, even though most results of clinical trials to date have been disappointing [41]. However, in a recent trial, treatment of SA patients with an IL-5 monoclonal antibody, mepolizumab, resulted in reduced OCS use [70]. Additional investigations with these agents should be performed, specifically in SA patients with an eosinophilia phenotype, to further define the potential benefits.

Effective add-on therapy for SA patients with non-eosinophilic inflammation is lacking. Macrolide antibiotics may be an option, as clarithromycin has been shown to modulate IL-8 and neutrophil levels and improve quality of life in SA patients with a noneosinophilic inflammatory profile [71•]. 5-Lipoxygenase inhibitors may inhibit neutrophilic activation and chemotaxis and have been postulated as a possible treatment for asthmatics with a predominant neutrophilic inflammation [41]. Lastly, blocking chemokines and their receptors may be beneficial given their role in attracting inflammatory cells to the airway; thus, chemokine receptor antagonists may be beneficial in SA with neutrophilic inflammation [41,72].

For SA with irreversible airflow limitation and evidence of airway remodeling, optimal treatment is not known. It may be that many of these changes are irreversible and unresponsive to treatment. In SA patients with evidence of remodeling, the addition of the dual long-acting bronchodilators salmeterol and tiotropium to moderate-dose ICS led to improved airflow and FE_{NO} in comparison with high- or moderate-dose ICS with just salmeterol [73]. These results suggest that the addition of multiple bronchodilators may improve lung function in patients with persistent airway obstruction.

A novel therapy called bronchial thermoplasty uses thermal energy through a bronchoscopic catheter to deplete hypertrophied airway smooth muscle. Bronchial thermoplasty has been studied in patients with SA with uncontrolled symptoms and has demonstrated marked improvements in subjective—but not objective—outcome measures in asthma control [74•]. A follow-up sham-controlled study of SA with this device was recently completed. This treatment would theoretically benefit patients with significant airway remodeling with isolated airway smooth muscle dysfunction and paucigranulocytic inflammation, but such a phenotype has not been studied with bronchial thermoplasty.

Previous work on potential steroid-sparing agents such as cyclosporine, intravenous immunoglobulin, gold, methotrexate, nebulized lidocaine, theophylline, tumor necrosis factor- α , and IL-5 has not led to dramatic changes in management strategies, although many have shown the ability to decrease corticosteroid use in small studies. Their role as corticosteroid-sparing agents should not be ignored, as the potential side effects of alternative

agents may be more manageable than those of high-dose corticosteroids. In addition, as some of these agents could prove beneficial if clinically, physiologically, or genetically identified subgroups of SA were defined that were more responsive to one of these treatments, it is important to consider their use in future trials.

Conclusions

There are multiple reasons why asthmatics can be difficult to control, including additional or complicating comorbidities and noncompliance. Once these factors are appropriately addressed, a group of genuine SA patients is identified and the true management challenge begins. It is not always clear if these patients are on a continuum of asthma severity that requires more intensive corticosteroid therapy or if they are a distinct entity that requires alternative therapy. Adding to the complexity is that this group is heterogeneous with distinct phenotypes and treatment implications. Unfortunately, current guidelines do not offer effective therapies for most SA patients. Given the lack of information to guide therapy in these patients with SA and that these patients are specifically those who have disproportionate health care utilization and impaired quality of life, a new emphasis on finding novel therapies with a low risk profile is needed for SA.

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