

Severe asthma: Epidemiology, burden of illness, and heterogeneity

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ABSTRACT

Background: Patients with severe persistent asthma comprise only 5–10 % of the total asthma population, but account for a large proportion of asthma morbidity and health care expenditures. Among patients with severe asthma, higher costs can be expected in association with not well or poorly controlled asthma.

Objective: To summarize the evidence concerning the epidemiology, burden, and heterogeneity of severe asthma.

Methods: A literature search was performed to identify citations using the terms “severe asthma” and “epidemiology”, “asthma control”, “asthma” and “heterogeneity”.

Results: Successful management of patients with severe asthma continues to be a major unmet need. One of the barriers to successful management is the heterogeneity of asthma. Asthma is not one disease; it is a disorder that can be subdivided into a number of different phenotypes and endotypes. A revised paradigm for asthma management, that entails categorization of asthma patients via use of “biomarkers”, and prescribing targeted therapy, will supplant what has been a “one size fits all” approach to asthma management.

Conclusion: The novel approach to asthma management, in which therapy will be more mechanism-specific based on phenotype/endotype, offers the potential for improved asthma care outcomes – particularly for patients with severe persistent asthma who are not well or poorly controlled.

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Epidemiology and Burden of Illness

Asthma has become increasingly common. Asthma now affects an estimated 25.9 million Americans.¹ Asthma has also become increasingly costly. Annual total (direct and indirect) medical expenditures for asthma were ~6.2 billion dollars in 1990.² The total cost of asthma to society in 2007 was estimated at 56 billion dollars.³

Patients with severe persistent asthma comprise only a minority (5–10%) of the total asthma population⁴ but account for a large proportion of asthma morbidity and health care expenditures.^{5,6} The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is a multicenter observational study that was designed to enhance our understanding of the natural history of severe or difficult-to-treat asthma.⁷ In the TENOR study cohort of 4756 patients, during the 3 months before enrollment, the proportion of adults, adolescents, and children who had at least one asthma hospitalization was 5, 10, and

9%, respectively, and the proportion who had emergency department management for asthma was 15, 17, and 22%, respectively. This remarkable rate of health service utilization was required despite high medication reliance. At enrollment, >55% of children, adolescents, and adults reported using three or more long-term asthma control medications. These findings are similar to outcomes of therapy observed in The Gaining Optimal Asthma Control study.⁸ Despite optimal medication use, in this case, combination controller therapy with inhaled corticosteroid and long-acting β -agonist, a substantial proportion of patients with asthma did not achieve control.

In recently published international guidelines,⁹ a task force from the European Respiratory Society and American Thoracic Society defined severe asthma as, “asthma which requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.” It is important to note that the concept of disease severity reflects not only an intrinsic characteristic of the disease in a particular patient but also its responsiveness to treatment.¹⁰

In contrast to other common conditions, such as hypertension, diabetes, or hypercholesterolemia, for which “biomarkers” exist to define targets for achieving control, asthma control does not lend itself to as straightforward a description and is best viewed as a multidimensional construct.¹¹ Asthma control may be

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assessed by use of validated instruments, including the Asthma Control Questionnaire, Asthma Therapy Assessment Questionnaire, and the Asthma Control Test. These instruments include assessment of daytime and nighttime asthma symptoms, frequency of dependence on “rescue” medication, the impact of asthma on everyday functioning, and, also, in the case of the Asthma Control Questionnaire, lung function.

The most recent guidelines from the National Asthma Education and Prevention Program¹² recommended that asthma management be carried out in an algorithmic manner. At the time of the initial presentation, the Third Expert Panel Report guidelines encourage providers to categorize patients into four severity categories, intermittent, mild persistent, moderate persistent, and severe persistent, based on assessments of the impairment (level of day-night symptoms, reliance on as-needed use of reliever medication, and lung function) and risk (exacerbations) domains. As illustrated in Table 1, assignment of “preferred” pharmacologic therapy was recommended according to each respective severity category, based on best evidence.¹² In an idyllic world, in which classification of patients with asthma would be carried out in a reliable fashion and adherence with management recommendations would be (close to) 100%, this would have resulted in patients with asthma receiving and regularly taking appropriate pharmacotherapeutic agents associated with favorable asthma care outcomes. However, in the real world this paradigm was flawed. It relied on accurate classification of patients for appropriate pharmacotherapy to be prescribed. Both providers and patients are prone to underestimate asthma severity^{13,14}; for this reason, many patients managed according to this paradigm were undertreated. Moreover, adherence in patients with asthma ranges from only 30 to 70%.¹⁵

The goal of asthma management is to achieve asthma control by reducing current impairment and safeguarding against future risk¹²; however, a number of studies indicate that, despite our improved understanding of asthma and the availability of better medications with which to treat it, a substantial proportion of patients with asthma have not well controlled or poorly controlled asthma.^{16,17} Although asthma costs are disproportionately higher in patients with severe persistent asthma,^{4,5} within this subgroup, even higher costs can be expected in association with not well controlled or poorly controlled asthma.^{18,19}

In a multicenter cross-sectional survey carried out at 35 primary care practices in the United States, 2238 patients with a self-reported physician diagnosis of asthma were invited to complete the Asthma Control Test in association with visiting their primary care provider.²⁰ The investigators divided these subjects into two groups: individuals in the office to seek care for a respiratory concern, and those in the office for other reasons (*e.g.*, annual physical, illness, injury). Among the subgroup seeking

care for respiratory symptoms, 72% were not well or poorly controlled. This is not unexpected. However, among those in the office for a nonrespiratory reason, 48% had not well controlled or poorly controlled asthma. In the absence of a valid and objective instrument with which to gauge asthma control, the almost 50% of patients seen in a primary care physician’s office for other reasons but who also have asthma would not be identified as being candidates for intervention based on having not well controlled or poorly controlled asthma. Patients with hypertension have their blood pressure checked routinely, regardless of the reason for an office visit. The findings of this study²⁰ imply that, similarly, a case can be made for advocating serial and routine assessment of asthma control for all patients with asthma in offices of asthma specialists as well as primary care providers, regardless of the reason for an office visit. Serial monitoring of asthma control can objectify the degree to which the goals of management as described in evidence-based guidelines are being achieved,²¹ and, in so doing, can encourage optimal asthma care outcomes.⁸

Asthma Is More Likely to be Severe and More Likely to be Poorly Controlled in African Americans

Among African Americans, asthma is more prevalent and more severe.²² African Americans are more likely to have not well controlled or poorly controlled asthma.^{20,22} The multiple influences that contribute to the ongoing disparities in asthma care outcomes among African Americans, which have been recently reviewed,²² include genetics, socioeconomic factors, cultural factors, health maintenance behaviors, and urban air quality. Obesity has been associated with a poorer response to inhaled corticosteroids and a higher risk of asthma exacerbations.^{23,24}

More than one-third of U.S. adults are currently obese, but obesity is 51% more prevalent in African Americans compared with whites.²⁵ Adherence rates are lower among African Americans compared with whites, even after adjusting for multiple socioeconomic variables.²⁶ In the TENOR study, the higher rates of emergency department visits for asthma, poorer asthma control, and greater impairment of quality of life observed in patients with severe asthma who were African American could not be explained with adjustment for a number of variables, including socioeconomic, disease severity, body mass index, aeroallergen sensitization, adherence, or treatment setting.²⁷ Another factor that contributes to poorer care outcomes is that asthma care providers are more likely to underestimate asthma severity in an African American patient than in a white patient,²⁸ which highlights the importance of improving provider-patient communication, specifically in managing patients with asthma

Table 1 The stepwise approach for management of asthma in individuals ages ≥ 12 years, recommended in Third Expert Panel Report guidelines, is displayed; the paradigm for asthma management recommends that asthma should be categorized initially by severity, with management assigned in an evidence-based manner, and that pharmacotherapeutic management decisions be based on the level of asthma severity*#

Severity Components	Intermittent	Persistent Asthma: Daily Medication			
		Mild	Moderate	Severe	
Symptoms	Less than once a week	More than twice per week but not daily	Daily	Throughout the day	Step-up if needed (first, check adherence, environmental control, and comorbid conditions)
Nocturnal symptoms	Less than twice a day per month	Three to four times per month	More than once a week but not every night	Often every night per week	
Interference with activity	Brief exacerbations	Exacerbations may cause minor limitation of activity and sleep	Exacerbations more than twice a week and may cause some limitation of activity and sleep	Frequent exacerbations with marked limitation of physical activity	
SABA use	≤ 2 days per week	> 2 days per week but not daily and not more than once on any day	Daily	Several times per day	Assess control
Pulmonary function test	• Normal FEV_1 between exacerbations • $FEV_1 > 80\%$ predicted • $FEV_1:FVC$, normal	• $FEV_1 > 80\%$ predicted • $FEV_1:FVC$, normal	• $FEV_1 > 60\%$ but $< 80\%$ predicted • $FEV_1:FVC$, reduced 5%	• $FEV_1 < 60\%$ predicted • $FEV_1:FVC$, reduced 5%	
Recommended treatment strategy§	Step 1	Step 2¶	Step 3¶	Step 4 or 5 Step 4¶	Step down if possible (and asthma is well controlled for at least 3 mo)
	Preferred: SABA PRN	Preferred: Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline	Preferred: Low-dose ICS + LABA or medium-dose ICS Alternative: Low-dose ICS + either LTRA, theophylline, or zileuton Consider oral steroids	Preferred: Medium-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA, theophylline, or zileuton Step 5 Preferred: High-dose ICS + LABA and consider omalizumab for patients who have allergies Consider oral steroids	

SABA = short acting β agonist; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PRN = as needed; ICS = inhaled corticosteroid; LABA = long acting β agonist; LTRA = leukotriene receptor antagonist; EIA = exercise induced asthma.

*Adapted from Ref. 12. Adapted from National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08–4051, 2007.

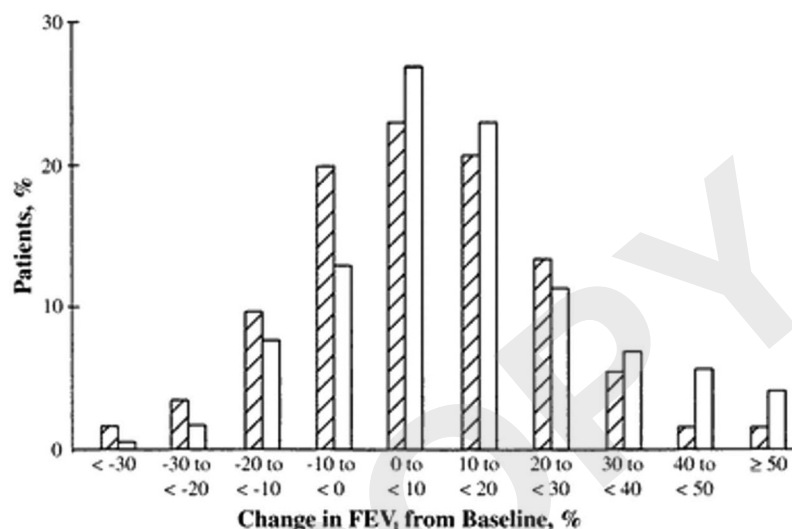
#Quick-relief medication for all patients:

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA > 2 days a week for symptom relief (not prevention of EIA) generally indicates inadequate control and the need to step up therapy.

§Each step: Patient education, environmental control, and management of comorbidities.

¶Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

Figure 1. Distribution of responses for forced expiratory volume in 1 second (FEV₁) in subjects randomized to montelukast 10 mg/day (striped bars) or inhaled beclomethasone 200 µg twice a day (white bars). In each treatment group, there was a heterogeneous distribution of responses.



who are African American. It is likely that a number of the above-mentioned factors are acting together, rather than separately, to influence the development and course of asthma in African Americans.

Heterogeneity

A major factor that contributes to the gap between the goals of asthma management as described in the Third Expert Panel Report guidelines and outcomes of normative asthma care in the community has become increasingly apparent in recent years: asthma is a heterogeneous disorder. Asthma is not one disease. It is a disorder that can be subdivided into a number of different phenotypes and endotypes.

In a review that appeared in *The New England Journal of Medicine* in 2012, a simulated encounter of a patient with asthma was described in three different years: 1828, 1928, and 2012.²⁹ The snapshot described of the care for asthma in 1828 was remarkable for this statement, “In the early 1800s, there were many ‘asthmatics’, since this was the term for any episodic shortness of breath.” Almost 3 centuries ago, physicians viewed asthma as heterogeneous. With the passage of time, this concept faded; however, based on recent evidence, it has now been reestablished.

In an article published in 1999, heterogeneity in response to two commonly prescribed medications for mild-moderate asthma was observed. In this study, 895 patients who were 15 to 85 years of age with chronic asthma, and a forced expiratory volume in 1 second (FEV₁) of 50 to 85% of predicted, were randomized to either placebo, oral montelukast 10 mg/day, or inhaled beclomethasone 200 µg twice daily for 12 weeks.³⁰ Overall, the improvement in FEV₁ for patients randomized to beclomethasone was 13.1%, for montelukast was 7.4%, and for placebo was 0.7% ($p < 0.001$ for each active treatment compared with placebo; $p < 0.01$ for beclo-

methasone compared with montelukast). As illustrated in Fig. 1, the subjects randomized to beclomethasone and to montelukast demonstrated a large degree of variation in response: some improved to a considerable extent, some improved to only a modest degree, some did not improve, and some worsened on therapy. These and other data have demonstrated that medication response is a phenotype.

Phenotypes and Endotypes

Asthma may be regarded as a collection of different disease variants that have the common presentation of “variable airflow obstruction.”³¹ An asthma phenotype describes a subgroup identified based on “clinically observable characteristics,” not necessarily related to underlying pathophysiology, triggers, or inflammatory parameters.³² Categorizing a patient with asthma based on phenotype, by using clinical features such as lung function, duration of asthma, the presence of wheal and/or flare reactions on immediate hypersensitivity skin testing, and response to therapy with a specific controller agent, may have utility for enhancing outcomes of asthma management. For instance, it would be important to identify aeroallergen avoidance measures that are appropriate based on skin test findings or the presence of an “exacerbation-prone phenotype.”³³ However, the classification of asthma by phenotype does not provide insight into or define a specific underlying disease process or pathologic mechanism.

An endotype is a mechanistically coherent disease subgroup defined by a distinct pathophysiologic mechanism.³⁴ An endotype may encompass several phenotypes; alternatively, certain phenotypes may represent more than one endotype. An asthma endotype is a subgroup of patients with a similar clinical presentation, epidemiology, and response to treatment.

Aspirin-exacerbated respiratory disease is an example of an asthma endotype. This subgroup of patients typically experiences adult-onset rhinosinusitis, followed by the development of asthma, and, when these two cardinal features of the “triad” have been established, casual exposure to aspirin or an aspirin-like drug provokes a respiratory reaction that may be serious or even life-threatening.³⁵ Patients with aspirin-exacerbated respiratory disease experience respiratory reaction to all agents that inhibit cyclooxygenase-1, exhibit overproduction of cysteinyl leukotrienes, and develop nasal and/or sinus polyps with impairment in sense of smell and taste. Patients with aspirin-exacerbated respiratory disease have benefited from an “endotype-driven” approach to management: they are likely to experience a salutary response to aspirin desensitization treatment, with statistically significant improvements in symptoms and quality of life, reduced formation of nasal and/or sinus polyps and episodes of sinusitis, less medication reliance, and fewer sinus surgery procedures over time.³⁵ There is no evidence that a salutary effect would be observed with aspirin administration in an individual with aspirin-tolerant asthma.

Asthma can be divided into two distinct molecular phenotypes, based on the level of T-helper type 2 (Th2) inflammation.^{36,37} “Th2 high” asthma is corticosteroid-responsive; however, as noted above, some patients do not achieve the goals of asthma management despite administration of corticosteroids with or without additional controller agents. Th2 high asthma is mediated by cytokines, including interleukin (IL)-4, IL-5, and IL-13. Biomarkers for the Th2 high phenotype, including measurement of peripheral blood eosinophils or exhaled nitric oxide, are widely available, and serum periostin should be available in the near future.³⁷ Analysis of recent data indicates that these biomarkers can identify individuals who are more likely to exhibit a salutary response in association with receiving a targeted therapeutic intervention.

Personalized Asthma Care: A Vision of the Future

In contrast to the algorithmic approach to asthma management recommended in the Third Expert Panel Report guidelines,¹² shown in Table 1, we are on the threshold of a new era in the management of asthma, particularly severe asthma. Rather than a “one size fits all” approach, with pharmacotherapeutic options directed by clinical parameters and a determination of level of severity, we will be able to prescribe targeted, mechanistically directed asthma therapy. The approach that looms around the next corner is consistent with a more personalized style of medical care. We will have the capacity to approach the complexity of severe asthma *a priori* to identify

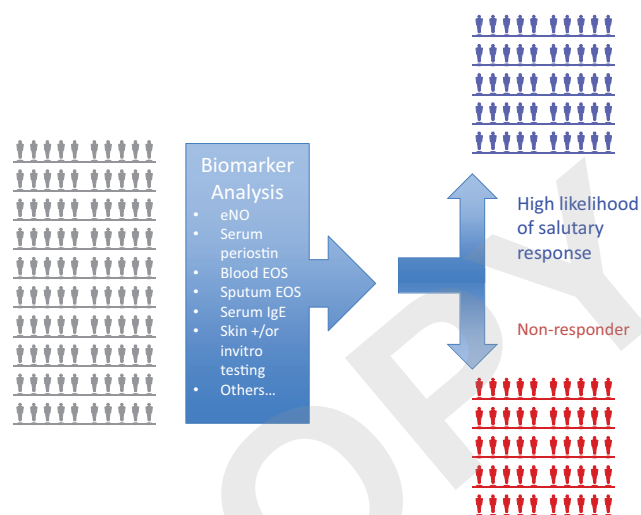


Figure 2. Of the 100 “patients” with severe persistent asthma that is poorly controlled, depicted on the left of this figure, ~50% are likely to experience a salutary response to a therapeutic agent. A validated biomarker can be used to identify the 50% who are likely to improve (shown in blue) and to select the 50% who are not likely to benefit (shown in red), so that the blue “patients” can proceed to receive the therapy and the red “patients” can be considered for alternative therapies.

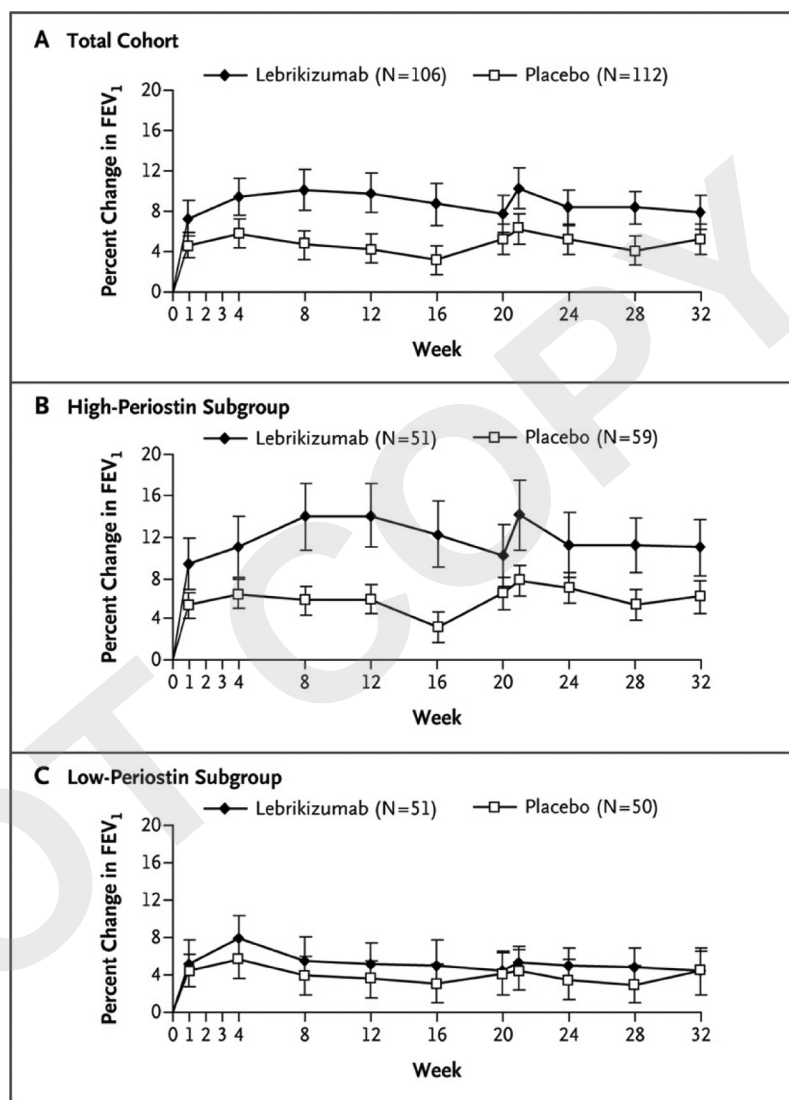
asthma subgroups (phenotypes and endotypes) more likely to have a salutary response to one or more therapeutic options.

This future approach to management of asthma is illustrated in Fig. 2. Of the 100 individuals with severe persistent asthma that is poorly controlled, depicted on the left in the figure, ~50% may have a salutary response to a therapeutic intervention; a biomarker is required to properly select those who are likely to benefit (shown in blue) and to allow others who are not likely to improve (shown in red) to be considered for alternative therapies. There is a need to identify and validate noninvasive biomarkers that can specifically direct medical decision-making so that asthma therapy can be appropriately targeted.

Serum immunoglobulin E and documentation of wheal and/or flare reaction to a perennial allergen are commonly used to properly select patients with poorly controlled severe persistent asthma who are candidates for a therapeutic trial of omalizumab.³⁸ In a recent report, three markers of the Th2 high phenotype, serum periostin, exhaled nitric oxide, and peripheral blood eosinophils, were used to categorize subjects who received omalizumab as “high” and “low” for each biomarker.³⁹ The treatment effect of omalizumab was superior (greater reduction in exacerbation rates) in subjects who were “high” for each biomarker, which implies that subjects identified as Th2 high *via* these biomarkers are likely to benefit to a greater extent on omalizumab.

A number of biologic agents for asthma will soon be available for clinical use,⁴⁰ including those that target IL-13

Figure 3. (A) The change in forced expiratory volume in 1 second (FEV₁) at week 12 in subjects randomized to lebrikizumab was 5.5% higher (95% confidence interval [CI], 0.8–10.2) compared with subjects in the placebo group (mean $\pm$ standard error [SE] change, $9.8 \pm 1.9\%$ vs $4.3 \pm 1.5\%$; $p = 0.02$). (B) In subjects who were “periostin high,” the increase from baseline FEV₁ was 8.2% higher (95% CI, 1.0–15.4) in those randomized to lebrikizumab compared with the placebo group (mean $\pm$ SE change, $14.0 \pm 3.1\%$ vs $5.8 \pm 2.1\%$; $p = 0.03$). (C) In subjects who were “periostin low,” the increase from baseline FEV₁ was only 1.6% higher (95% CI, -4.5 to 7.7) in those randomized to lebrikizumab compared with the placebo group (mean $\pm$ SE change, $5.1 \pm 2.4\%$ vs $3.5 \pm 2.1\%$; $p = 0.61$).



or IL-4 (lebrikizumab, tralokinumab, dupilumab) and IL-5 (mepolizumab, reslizumab, benralizumab). Consistent with the schema shown in Fig. 2, when subjects were categorized by using a biomarker, serum periostin, to identify those subjects with a Th2 high phenotype, as shown in Fig. 3,⁴¹ the subjects who were “periostin-high” and who were randomized to lebrikizumab exhibited statistically significant improvement in FEV₁ compared with subjects randomized to placebo. Statistically significant improvement in FEV₁ was not observed in subjects who were “periostin low” who received lebrikizumab. Similarly, when mepolizumab was investigated in early studies in which subjects were not selected based on markers of eosinophilic airway inflammation, no remarkable improvements in clinical asthma end points were observed.⁴² More recently, mepolizumab has been associated with statistically significant benefit in asthma outcomes in the context of the approach shown in Fig. 2, with subject selection carried out based on elevated levels of peripheral blood eosinophils.⁴³

Summary

Patients with severe persistent asthma comprise only 5–10% of the total asthma population but account for a substantial proportion of asthma morbidity and health care expenditures. Successful management of patients with severe asthma continues to be a major unmet need. One of the barriers to successful management is the heterogeneity of asthma; more specifically, the lack of an ability to categorize a patient based on phenotype and/or endotype, and to prescribe targeted therapy. We are approaching a new era in the management of asthma. A revised paradigm for asthma management that entails categorization of patients with asthma *via* the use of a “biomarker” and prescribing mechanism-specific therapy will supplant what has been a “one size fits all” approach to asthma management. This novel approach to asthma management offers the potential for improved asthma care outcomes, particularly for patients with severe persistent asthma with not well controlled or poorly controlled asthma.

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