For more than a century, clinicians have attempted to subdivide asthma into different phenotypes based on triggers that cause asthma attacks, the course of the disease, or the prognosis. The first phenotypes that were described included allergic asthma, intrinsic or nonallergic asthma, infectious asthma, and aspirin-exacerbated asthma. These phenotypes are being reviewed elsewhere in this issue of the journal. The present article focuses on developing and emerging clinical asthma phenotypes. First, asthma phenotypes that are associated with environmental exposures (occupational agents, cigarette smoke, air pollution, cold dry air); second, asthma phenotypes that are associated with specific symptoms or clinical characteristics (cough, obesity, adult onset of disease); and third, asthma phenotypes that are based on biomarkers. This latter approach is the most promising because it attempts to identify asthma phenotypes with different underlying mechanisms so that therapies can be better targeted toward disease-specific features and disease outcomes can be improved. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:671-80)

**Key words:** Asthma; Phenotypes; Occupational asthma; Cigarette smoke-induced asthma; Air pollution-induced asthma; Exercise-induced asthma; Exacerbation-prone asthma; Persistent airflow limitation; Cough-variant asthma; Adult-onset asthma; Obesity; Eosinophilic asthma; Neutrophilic asthma; Review

The importance of subphenotyping asthma has been recognized by clinicians for more than a century and has evolved from trigger-induced phenotypes, such as allergen-induced asthma and aspirin-exacerbated asthma, via phenotypes based on clinical symptoms (eg, exacerbation-prone asthma, asthma with fixed airflow limitation) to phenotypes distinguished by

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No funding was received for this work.

Conflicts of interest: P.-P. Hekking has received consultancy fees from Novartis. E. H. Bel is on the Novartis board; has received consultancy fees from Glaxo-SmithKline, Regeneron, and CIPLA; has received research support from Chiesi, GlaxoSmithKline, and Novartis; and has received lecture fees from GlaxoSmithKline.

Received for publication August 12, 2014; revised September 19, 2014; accepted for publication September 21, 2014.

Available online October 5, 2014.
biomarkers (eg, eosinophilic asthma, noneosinophilic asthma). Many subjects with asthma have uncontrolled disease, which is associated with a high economical burden and impaired quality of life. Therefore, successful treatment is crucial and requires correct diagnosing and characterizing of the disease. Because asthma is a heterogeneous disease, phenotyping is an important step toward better treatment approaches and ultimately personalized medicine.

Apart from the clinical asthma phenotypes that are described elsewhere in this issue of The Journal of Allergy and Clinical Immunology: In Practice (eg, allergic asthma, aspirin-exacerbated asthma, nonallergic asthma, infection-related asthma, and the childhood preasthma phenotype, many other clinical asthma phenotypes are described in the literature. Most of these clinical phenotypes are ill defined and difficult to identify as separate entities, and little, if anything, is known about their underlying pathophysiology. These other clinical phenotypes are classified into “trigger-induced phenotypes,” “symptom-based phenotypes,” and “biomarker-based phenotypes” in this review.

TRIGGER-INDUCED ASTHMA PHENOTYPES

Occupational asthma

Occupational asthma is a clinically distinguishable asthma phenotype caused by exposures in the workplace and is different from work-exacerbated asthma, which is preexisting or concurrent asthma worsened by work-related factors. Risk factors for some types of occupational asthma include atopy and genetic factors. Smoking also may play a role in the onset of occupational asthma. Occupational asthma can be caused by sensitizers (sensitizer-induced occupational asthma) or irritants (nonsensitizing occupational asthma). With sensitizer-induced occupational asthma, subjects become sensitized to either high-molecular-weight (>10 kD) or low-molecular-weight agents (<10 kD). Hundreds of distinct causes of occupational asthma are recognized.

High-molecular-weight agents, usually proteins, cause an allergic immunologic response with specific IgE antibodies. This type of occupational asthma often is associated with allergic rhinitis. Low-molecular-weight agents usually are chemicals (eg, diisocyanates). The mechanism of low-molecular-weight agent-induced asthma is still not understood. Subjects with occupational asthma have respiratory symptoms that begin at the start of the workday, progress during the day, and, in some cases, persist during the evening. Typically, symptoms remit during weekends and holidays. Workers first need to be sensitized, which can take weeks to years, before symptoms occur with exposure to the incriminated agent, in this case, a sensitizer. Approximately 10% of all workers who are exposed to sensitizing agents eventually develop occupational asthma.

“Nonsensitizing occupational” asthma or irritant-induced occupational asthma is caused by exposure to airway irritants at the workplace. Sensitization is not involved, and, therefore, there is no latency period. This type of occupational asthma occurs, for example, with workers exposed to cleaning products and farmers exposed to ammonia and organic dust. The clinical presentation, prevention, and treatment of work-exacerbated asthma are similar to that of sensitizer-induced occupational asthma. The diagnosis of occupational asthma is based on careful history taking and serial peak flow measurements after exposure and after 2 weeks of no exposure. Specific inhalation challenge is the criterion standard, although this method is underused because of a scarcity of facilities or concerns about risks of doing the challenge test. Studies that use inflammatory cells in sputum or exhaled nitric oxide (FeNO) are of limited value to diagnose occupational asthma, although the latter may be of value in predicting clinical outcomes. The exact prevalence of occupational asthma is unknown and varies among occupations, although it is estimated that up to 15% of all new-onset asthma in adults is work related.

Cigarette smoke–induced asthma

Cigarette smoke can aggravate asthma symptoms and worsen disease control. Subjects with asthma and who smoke exhibit more cough and phlegm and have more unscheduled health care visits, and receive more rescue oral corticosteroids. Furthermore, they exhibit a more rapid decline in lung function and their asthma is more refractory to oral and inhaled corticosteroids. In addition, smoking increases the severity of asthma. Astonishingly, the prevalence of smokers with asthma is similar to that of smokers without asthma, between 20% and 35%. There is increasing evidence that exposure to cigarette smoke also can be a cause of asthma. Population cohort–based studies found a higher prevalence of asthma and airway hyperresponsiveness with the smoking population. In adults with allergy, smoking is predictive for new-onset asthma and, among subjects with new-onset asthma, those with a positive smoking history develop more severe asthma. Analysis of these data suggests that specific substances in cigarette smoke may activate pathways similar to other sensitizers such as allergens or low-molecular-weight chemicals. This hypothesis is supported by the observation that smoking when having asthma is associated with higher IgE levels, which resembles the immune response of subjects with atopic asthma.

Also, passive exposure tobacco smoke is associated with the development and severity of asthma in children. Regular smoking increased the risk for asthma among adolescents, especially for adolescents without allergy and for those exposed to maternal smoking during the in utero period. A post-hoc analysis of the children cohort of The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens study found 5 clusters of children with difficult-to-treat or severe asthma, one of which could be distinguished by smoke exposure. Even maternal smoking during pregnancy may play a role in the onset of asthma in children. Two large longitudinal follow-up studies of 14 and 20 years, respectively, demonstrate that maternal smoking during pregnancy is an important risk factor for the development of asthma in the offspring. An important finding is that approximately 50% of pregnant women who smoke will not quit during pregnancy. Thus, although the cigarette smoke–induced asthma phenotype is not yet widely accepted, there is sufficient evidence that cigarette smoke aggravates the course of the disease and plays a role in the onset of asthma in both children and adults.
Air pollution–induced asthma

Air pollution–induced asthma is even less recognized than cigarette smoke–induced asthma. Airborne pollution, in particular, outdoor pollution produced by industry and by air and road traffic is known to worsen asthma control and contribute to the development of new-onset disease. A European study estimates that the 14% incidence of asthma and 15% of asthma exacerbations in childhood are related to exposure to road traffic pollutants. Similar to occupational agents and cigarette smoke, outdoor air pollution seems to contribute to asthma in 2 ways: first, as an aggravating factor, and second, as a cause of asthma. Traffic pollutants have the highest concentration within 150 m from a road. This concentration remains high up to 300 m, after which it markedly declines. Epidemiologic studies have used these figures to confirm the hypothesis that traffic air pollution plays a role in the development of asthma in both children and adults. These studies found a higher prevalence of wheezing illness in children who live within 100 m of a main road as well as in children going to school under the same conditions. Furthermore, air traffic pollution correlates with adult-onset asthma among never-smokers, which resembles the findings of studies that investigated the effect of exposure to other toxic substances, such as cigarette smoke and low-molecular occupational agents.

Pollutants, such as ozone, nitrogen oxide, and particulate matter <2.5 μm in diameter, can induce airway hyperresponsiveness and neutrophilic airway inflammation; however, the mechanism is unknown. Probable air pollutants cause oxidative injury to the airways, which leads to inflammation, remodeling, and increased risk of sensitization. Whether air pollution–induced asthma represents a separate subphenotype remains to be confirmed. If so, this phenotype may become more common in future decades, secondary to more global urbanization.

Exercise-induced asthma

Exercise-induced asthma, also referred to as exercise-induced bronchoconstriction, occurs with subjects with asthma of any phenotype or severity and is caused by the cooling and drying of the airways associated with exercise, a potent stimulus for bronchoconstriction. The phenotypic term “exercise-induced asthma” however, mostly refers to elite athletes who develop bronchoconstriction with prolonged and severe exercise but who never had asthma before. Long-term intense endurance training by elite athletes, particularly under certain environmental conditions, is associated with an increased risk of developing asthma and airway hyperresponsiveness. For example, Olympic cross-country skiers are constantly exposed to dry and cold air, whereas ice rink athletes and competitive swimmers are exposed to indoor pollutants. Long-distance runners can be exposed to high levels of aerosol allergens and ozone. Elite athletes often have airway neutrophilic or eosinophilic airway inflammation, depending on the type of sport.

Clinical symptoms of exercise-induced asthma include wheezing, shortness of breath, dyspnea, cough, or chest tightness 5 to 10 minutes after exercise. The diagnosis is based on a ≥10% decrease in FEV1 within 30 minutes after exercise in comparison with pre-exercise FEV1. It can be followed by a refractory period which can persist for 4 hours, during which exercise causes less bronchoconstriction. Symptoms can be reversed with short-acting β2-adrenergic agonists. The prevalence of exercise-induced asthma with elite athletes varies from 10% to 50% with those without existing asthma and occurs up to 90% with those with preexisting asthma. These numbers may be exaggerated because elite athletes might have a different perception of dyspnea than nonelite athletes, which results in a higher prevalence of the disease.

SYMPTOM-BASED PHENOTYPES

Exacerbation-prone asthma

This asthma phenotype is characterized by frequent asthma exacerbations defined as episodes of “worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome.” There is no consistent definition of “frequent” exacerbations, but more than 2 or 3 during a year is commonly used, as included in the 2014 International Guidelines on Severe Asthma. These exacerbations account for a large economic and physical burden for the patient and health care system. Annually, nearly 500,000 hospitalizations and 2,000,000 emergency department visits are due to asthma exacerbations in the United States. Therefore, distinguishing a phenotype characterized by frequent exacerbations in mild, moderate, and severe asthma seems important.

The diagnosis of the exacerbation-prone asthma phenotype relies primarily on a history of frequency of the use of oral corticosteroids, emergency department visits, and hospitalizations. Characteristics of subjects with frequent exacerbations were first described by in’t Veen et al in 2000 who demonstrated that frequent exacerbators versus those with equally severe stable asthma had more peripheral airway obstruction. Results of another study showed that such subjects with difficult-to-treat asthma and recurrent exacerbations had more comorbidities, including chronic rhinosinusitis, recurrent respiratory tract infections, obesity, obstructive sleep apnea, and psychopathology. The identification of frequent exacerbators as a separate phenotype was confirmed from a cluster analysis of a severe asthma population by the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program. They found 1 cluster to be characterized by frequent exacerbations and persistent eosinophilic inflammation both in the blood and bronchoalveolar lavage fluid despite the use of high doses of systemic corticosteroids. The analysis of subjects with difficult-to-treat asthma in The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens study, as well as several other studies, shows that the exacerbation rate is independently associated with a risk for a future exacerbation, which suggests that this asthma phenotype is consistent over time. The prevalence of the exacerbation-prone asthma phenotype is unclear; however, a recently published study found that 30% of subjects with severe asthma and 2.5% of those with mild-to-moderate asthma were frequent exacerbators.

Asthma with persistent airflow limitation

Persistent airflow limitation as a key characteristic of a specific asthma phenotype was first suggested by ten Brinke et al and confirmed by cluster analysis studies in both Europe and the United States. This type of asthma is characterized by “fixed airflow limitation,” defined as airflow limitation that is not fully reversible after administration of a bronchodilator; it may improve after treatment with high doses of systemic corticosteroids. Subjects with persistent airflow limitation often have adult-onset asthma, are men, nonatopic, with few daily symptoms, and persistent sputum eosinophilia. Results of some studies have
indicated that infection with *Chlamydia pneumonia* might be an underlying cause of an accelerated decline in lung function with asthma. The phenotype must be distinguished from subjects with asthma who have persistent airflow limitation due to factors other than eosinophilic inflammation, such as tobacco smoke or occupational exposures, a reduced lung function at the beginning of adult life, and long-standing asthma.

Several studies of subjects with severe or difficult-to-control asthma as well as adult-onset asthma showed varying prevalences of this phenotype of up to 60%,. There is evidence that an "exacerbation prone asthma phenotype" might eventually evolve into a "fixed airflow limitation phenotype" because frequent exacerbations are associated with a more rapid decline in FEV1.

Cough-variant asthma

Cough is a common symptom of asthma, and, although it usually accompanies other symptoms, such as wheeze and dyspnea, it may present and remain the sole symptom. This subtype is known as "cough-variant asthma." Subjects with cough-variant asthma are thought to represent a different phenotype from those with classic allergic asthma or with eosinophilic bronchitis. This is based, first, on the absence of dyspnea and wheezing, and, second, on the presence of mast cells located in airway smooth muscle, which has been shown to be associated with airway hyperresponsiveness. The demonstration of airway hyperresponsiveness to nonspecific stimuli, eosinophilic airway inflammation, and a favorable response to asthma treatment, therefore, is key to the diagnosis of this phenotype.

Multiple studies show that 30% to 60% of adult subjects who are nonsmoking and with chronic cough have cough-variant asthma.

Adult-onset asthma

Many studies identified adult-onset asthma as a separate phenotype, either by clinical observation or by using supervised and unsupervised cluster analysis. An editorial in *The Lancet* in 1971 indicated that adult-onset asthma should be distinguished from childhood-onset asthma. Adult-onset asthma has a more chronic course and is more often nonatopic than is childhood onset asthma; sputum eosinophilia is associated with both types. In contrast to childhood-onset asthma, the frequency of exacerbations does not fall with increased age and the prognosis is worse. Other studies confirmed that subjects with adult-onset asthma are less often atopic and have a more rapid decline in lung function, lower remission rates, and a poorer prognosis. Miranda et al in 2004 showed that subjects with childhood-onset severe asthma had significantly more allergen sensitivity and allergic symptoms than did subjects with late-onset (>13 years of age) asthma. In contrast, subjects with late-onset severe asthma had lower lung function despite a shorter duration of illness. Those with persistent eosinophils in bronchial biopsy specimens of either age of onset had significantly more asthma symptoms. Haldar et al and the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program study group used cluster analysis to identify asthma phenotypes. They found 2 different late-onset asthma phenotypes, one characterized by obesity and female sex, and the other by active airway inflammation, fixed airflow limitation, male sex, and longer duration. Because adult-onset asthma has a low remission rate and often is more severe, a large proportion of subjects with severe asthma develop their disease in adulthood. The prevalence of those with late-onset asthma in tertiary care centers can be as high as 40% of the total asthma population (E.H.B., personal observation).

The obese asthma phenotype

The prevalence of obesity and asthma has increased over the past decade, and many studies investigated the relationship between these 2 conditions, reviewed elsewhere. They showed an increased prevalence of asthma with subjects who were obese and those who were overweight, which led to the general acceptance that obesity (body mass index [BMI] > 30 kg/m²) represents a separate phenotype. At least 3 different cluster analyses show that obesity is a distinguishing feature of a specific phenotype, particularly with women with adult onset disease. This fits in with the observation that obesity also is a risk factor for new-onset asthma of adolescents.

Several population studies found the odds ratio for asthma to be between 1.6 and 3.0 in obese adults. The incidence is linearly related to the BMI: that is, the higher the BMI, the higher the risk for developing asthma. The risk of obesity-associated asthma was higher for women than for men and in nonobese versus atopic asthma. Also, a higher weight in children is associated with a higher risk of asthma. This is an even stronger clinical determinant for developing asthma than other clinical, physiologic, or inflammatory variables. Subjects with the obese asthma phenotype lack the eosinophilic airway inflammation and are often difficult to control with variable responses to conventional medical therapies. In fact, results of studies showed that the BMI is inversely related to sputum eosinophilia and FeNO and positively associated with the presence of comorbid factors and reduced lung function. The prevalence of patients with asthma and with a BMI ≥ 30 kg/m² was 21% in a Dutch cohort of difficult-to-treat or severe asthma, whereas it was 48% in the United Kingdom in a similar group.

BIOMARKER-BASED PHENOTYPES

Noninvasive markers of airway inflammation found in bronchial biopsy specimens, induced sputum, peripheral blood, or exhaled air also are used to identify asthma phenotypes that may require specific targeted therapies.

Eosinophilic asthma

Eosinophilic airway inflammation occurs in all age groups, in moderate-to-severe asthma, and in association with allergic as well as nonallergic phenotypes. The term "eosinophilic asthma" refers to asthma with elevated eosinophils in bronchial biopsy specimens, induced sputum, or peripheral blood, with or without concomitant therapy with inhaled corticosteroids. In subjects who were corticosteroid naive, eosinophilic asthma is defined as the presence of ≥2% eosinophils of the total white blood cell count in induced sputum, whereas, with subjects on high-dose inhaled corticosteroid treatment, thresholds from 2% to 4% are used to identify this phenotype. Because of the limited access to sputum, peripheral blood eosinophilia is increasingly used to identify the eosinophilic asthma phenotype. A 2014 study of subjects with uncontrolled asthma on maintenance inhaled corticosteroid therapy identified the optimum cutoff point for the presence of blood eosinophilia at 2.7% and the absolute blood eosinophil...
count at 260 cells/μL, although eosinophil counts as low as 150 cells/μL also have been proposed. Surprisingly, peripheral blood eosinophilia appears to be a better predictor of response to the anti–IL-5 antibody mepolizumab than does sputum eosinophilia.

Studies that used cluster analyses identified an eosinophilic asthma phenotype and even distinguished between 2 different eosinophilic phenotypes: 1 with concordance between symptoms and airway eosinophilia, characterized by childhood-onset and allergy to airborne allergens (“early onset allergic asthma”), and 1 with discordance between symptoms and airway eosinophilia, characterized by few symptoms, late-onset nonatopic disease, and with or without persistent airflow limitation (“late-onset eosinophilic asthma”). The eosinophilia in this latter category appears to be most refractory to inhaled corticosteroids. It is suggested that the eosinophilia in these 2 phenotypes is mediated by different nonmutually exclusive pathways. The first one is driven by allergen-specific adaptive Th2 cells, and the second one is driven by allergen-independent innate lymphoid cells. Both produce IL-5 on stimulation, a cytokine that recruits eosinophils from the bone marrow and promotes the persistence and activation of these cells.

The presence of eosinophils in subjects on high-dose inhaled or oral corticosteroids is often associated with symptomatic and exacerbation prone disease. Dosing of inhaled or oral corticosteroids based on the level of eosinophils in sputum decreases exacerbations compared with standard guidelines—based assessments, which strengthens the eosinophil-exacerbation link. This improvement in clinical parameters, specifically associated with reduction in eosinophils, was confirmed in a series of studies with the IL-5 antagonist mepolizumab, in which reductions in sputum eosinophils decreased the number of severe exacerbations and permitted corticosteroid tapering.

Eosinophilia in “late-onset eosinophilic asthma” is strongly associated with aspirin sensitivity, chronic rhinosinusitis, and nasal polyps. Analysis of the data also suggests that persistent eosinophilic inflammation versus “non-eosinophilic asthma” is associated with a lower BMI.

The prevalence of eosinophilic asthma in different studies ranges from 36% to 67% of subjects who were inhaled corticosteroid naive and 17% to 39% of subjects who were treated with inhaled corticosteroid. However, the prevalence in severe asthma may be as high as 45%. Patients with this phenotype continued to have eosinophilic airway inflammation after 5 to 6 years, which suggests persistent underlying mechanisms. However, the numbers of eosinophils may decrease if the doses of systemic corticosteroids are high enough, which results in the eosinophilia being missed. Fluticasone in asthma severity or medication usage might affect the stability of the eosinophilic phenotype, which underscores the importance to assess asthma phenotypes over a prolonged period of time.

**Role of FeNO to identify the eosinophilic phenotype.** Because there is a significant correlations between sputum eosinophil counts and FeNO levels in patients with allergic asthma, FeNO is used as a noninvasive test to indirectly

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**FIGURE 1.** Theoretical grouping of asthma phenotypes in adulthood, divided by period of onset and by eosinophilic versus non-eosinophilic airway inflammation.
Role of periostin in identifying the eosinophilic phenotype. Periostin, an extracellular matrix protein that is induced by IL-4 and IL-13 in airway epithelial cells and lung fibroblasts has been proposed as a biomarker for eosinophilic airway inflammation.179 Periostin has been used successfully to identify Th2-high and Th2-low phenotypes, based on the levels of total IgE and blood eosinophils.180 Targeting IL-13 with lebrikizumab for subjects with high Th2 resulted in improvement in the FEV1 and reduction in FeNO as well as asthma exacerbations, which was most evident in the high-periostin subgroup.177 Analysis of these data indicates that serum periostin might be a useful biomarker to identify subjects with asthma who would be most responsive to anti–IL-13 therapies. However, the association of periostin with airway eosinophilia induced by allergen-independent pathways remains to be confirmed.

Neutrophilic asthma

Neutrophilic inflammation has been demonstrated with subjects with persistent asthma of varying severities and is defined by using induced sputum cell counts, with thresholds that ranged from 41% to 61% of total cells.147,178 However, the existence of the “neutrophilic phenotype” is controversial.165,181 Misclassification of inflammatory phenotypes may easily occur due to confounding factors, such as concurrent corticosteroid use, smoking, age, air pollution, occupation, high-grade exercise, respiratory infection, sensitization to Aspergillus, and gastro-esophageal disease.165,182-18 One study showed that a pure neutrophilic asthma phenotype could not be identified after withdrawal of inhaled corticosteroids for nonsmoking adults with moderately severe stable asthma.165 Reinstatement of inhaled corticosteroid treatment with these subjects was associated with increased airway neutrophils and a switch to a neutrophilic phenotype.165

Compared with eosinophilic asthma, noneosinophilic asthma is less responsive to corticosteroid treatment.11,164,188 Neutrophilic airway inflammation is reported to be more prevalent with older than with younger subjects.183 Compared with sputum eosinophilia, sputum neutrophilia is associated with a higher BMI with subjects with mild-persistent asthma.164 In severe asthma increased numbers of neutrophils in induced sputum are associated with air trapping as seen on computed tomography.189,190 Similarly, a relationship between sputum neutrophilia, asthma duration, and persistent airflow limitation has been observed.191

The prevalence of neutrophilic asthma depends largely on its severity. Data from 995 subjects with asthma who were enrolled in the Asthma Clinical Research Network clinical trials showed that 46% of subjects who were glucocorticoid naive and with mild-moderate persistent asthma had persistent noneosinophilic asthma of whom approximately half had >40% sputum neutrophils.164 Sputum neutrophilia, with or without eosinophilia, appears to be more common in severe asthma.129,192 Subjects in the the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program study showed that the vast majority with severe asthma had high percentages of neutrophils and that a large proportion also had persistently elevated percentages of eosinophils, which suggests that single biomarkers such as sputum eosinophils or neutrophils alone are unlikely to be sufficient to accurately identify the phenotype of subjects with severe asthma.193 This fits with the observation that CXCR2 antagonists that inhibit the recruitment and activation of neutrophils show only modest improvements of control of severe asthma.194 However, macrolides show a beneficial effect with subjects with predominant neutrophilic asthma, possibly because of their direct or indirect antimicrobial effects.195

CONCLUSION AND FUTURE PERSPECTIVES

Identifying the phenotype of asthma, based on environmental triggers or clinical features, is valuable because it enables physicians to advise their patients about avoidance measures and selected treatment programs that benefit 1 phenotype more than another. It also enables them to inform patients about the expected course and outcome of their disease. The advent of the use of inhaled corticosteroids in the 1960s was a breakthrough in asthma management, but not all asthma phenotypes respond equally well, which emphasizes the need for a better understanding of the underlying mechanisms that cause this disparity. Although clinical defining phenotypes provides some important clues about underlying mechanisms and has led to the identification of targets for novel treatments in some subphenotypes, there still is a large proportion of subjects whose asthma remains inadequately controlled. Therefore, it is essential to continue investigating underlying molecular abnormalities that cause these various phenotypes.171 It also should be recognized that asthma phenotypes may overlap, with speculated relationships, as diagrammed in Figure 1. Collaborations between private and public research entities should support the continual quest to better define phenotypes of asthma.196

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