Review Article

Developing and Emerging Clinical Asthma Phenotypes

Pieter-Paul W. Hekking, MD, and Elisabeth H. Bel, MD, PhD *Amsterdam, The Netherlands*

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;■:■-■)

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[1] and has evolved from trigger-induced phenotypes, such as allergen-induced asthma[2] and aspirin-exacerbated asthma,[3,4] via phenotypes based on clinical symptoms (eg, exacerbation-prone asthma,[5,6] asthma with fixed airflow limitation[7]) to phenotypes distinguished by biomarkers (eg, eosinophilic asthma,[8-10] noneosinophilic asthma[10,11]). Many subjects with asthma have uncontrolled disease, which is associated with a high economical burden[12,13] and impaired quality of life.[14] 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* i.e. 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.[15] 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[16] and is different from work-exacerbated asthma, which is preexisting or concurrent asthma worsened by work-related factors.[17,18] Risk factors for some types of occupational asthma include atopy[19] and genetic factors.[20] Smoking also may play a role in the onset of occupational asthma.[21] 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.[22]

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.[23] 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.[18]

"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.[24,25] The clinical presentation, prevention, and treatment of work-exacerbated asthma

The Department of Respiratory Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands

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 GlaxoSmithKline, 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 ■■

Corresponding author: Pieter-Paul W. Hekking, MD, Department of Respiratory Medicine, F5-260, Academic Medical Centre, University of Amsterdam, PO Box 22700, 1100DE, Amsterdam, the Netherlands. E-mail: p.w.hekking@amc.nl.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2014.09.007

Abbreviations used
BMI- Body mass index
FeNO- Exhaled nitric oxide

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.[26,27] Specific inhalation challenge is the criterion standard, although this method is underused because of a scarcity of facilities[28] or concerns about risks of doing the challenge test.[29] Studies that use inflammatory cells in sputum or exhaled nitric oxide (FeNO) are of limited value to diagnose occupational asthma,[30,31] although the latter may be of value in predicting clinical outcomes.[32] 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.[33,34]

Cigarette smoke–induced asthma

Cigarette smoke can aggravate asthma symptoms and worsen disease control.[35-37] Subjects with asthma and who smoke exhibit more cough and phlegm[38,39] and have more unscheduled health care visits, and receive more rescue oral corticosteroids courses.[36] Furthermore, they exhibit a more rapid decline in lung function[40,41] and their asthma is more refractory to oral and inhaled corticosteroids.[42,43] In addition, smoking increases the severity of asthma.[44,45] Astonishingly, the prevalence of smokers with asthma is similar to that of smokers without asthma, between 20% and 35%.[46,47] 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.[48-51] In adults with allergy, smoking is predictive for new-onset asthma,[45,52] and, among subjects with new-onset asthma, those with a positive smoking history develop more severe asthma.[44] 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,[53] 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.[54,55] 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.[50] 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.[56] Even maternal smoking during pregnancy may play a role in the onset of asthma in children.[57,58] 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.[59,60] An important finding is that approximately 50% of pregnant women who smoke will not quit during pregnancy.[61] 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.[62] 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.[63] Similar to occupational agents and cigarette smoke, outdoor air pollution seems to contribute to asthma in 2 ways: first, as an aggravating factor,[64-66] and second, as a cause of asthma.[67-72] 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.[73] 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.[67-72] 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.[71] Furthermore, air traffic pollution correlates with adult-onset asthma among never-smokers,[69] 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,[74] nitrogen oxide,[75] and particular matter <2.5 μm in diameter,[76] 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.[62] 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.[77] 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.[77] 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.[78-82] For example, Olympic cross-country skiers are constantly exposed to dry and cold air,[83] whereas ice rink athletes and competitive swimmers are exposed to indoor pollutants.[81,84] Long-distance runners can be exposed to high levels of aeroallergens and ozone.[85] Elite athletes often have airway neutrophilic or eosinophilic airway inflammation, depending on the type of sport.[86-88]

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 $\geq$10% decrease in FEV_1 within 30 minutes after exercise in comparison