Update in Asthma 2011

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The prevalence of asthma in the United States has increased by 12% since 2001 (1). Variability in response to guideline-based therapy has been increasingly recognized. Exciting clinical advances in 2011 related to biomarker-targeted asthma treatment. There were also reports on advances in the understanding of potential immune, cellular, and biochemical mechanisms that contribute to asthma pathobiology, work in defining genetic contributors to asthma, and elucidation of environmental factors that can influence the development or expression of the disease. This review summarizes relevant articles in the *Journal*, along with several pertinent studies published elsewhere in 2011.

ASTHMA TREATMENT

Reassessment and Optimization of Existing Therapies

In 2010, many treatment-related articles focused on the safety of long-acting β-agonists (LABAs) (2). The U.S. Food and Drug Administration has mandated that the producers of LABAs undertake large studies including tens of thousands of patients to address the question of whether LABAs increase the risk of asthma-related hospitalizations or deaths when used with concomitant inhaled corticosteroid (ICS) therapy. The results of these studies will not be available for 4–5 years at the earliest. Meanwhile, a retrospective analysis in 2011 of participants in studies conducted by the NHLBI's Asthma Clinical Research Network suggested that blacks may experience increased deteriorations when treated with LABAs (3). When Wechsler and colleagues analyzed studies performed by the Asthma Clinical Research Network that included a LABA, they found that blacks had increased rates of asthma treatment failure as compared with whites regardless of concomitant ICS therapy. No such differences occurred in studies without LABAs.

In 2011, several studies examined the efficacy of differing asthma treatment approaches to minimize adverse events. Two studies suggested that intermittent ICS use might be as beneficial as regular ICS use in children. The TREXA (TReating Children to Prevent Exacerbations of Asthma) study found that if 5- to 18-year-olds with mild asthma used ICS each time they used albuterol, asthma control did not differ significantly from daily ICS use. A strong disincentive to use daily ICS was that it was associated with a 1.1 cm decrease in linear growth over a year (4). In a study called MIST (Maintenance Versus Intermittent Inhaled Steroids in Wheezing Toddlers), the same group reported that in toddlers with a positive modified asthma predictive index and a history of wheezing, symptom-initiated high-dose budesonide inhalation over 7 days was as effective as daily lower-dose budesonide therapy, and resulted in a 70% reduction in ICS use (5). No growth differences were noted in this young population.

Although most studies have not suggested adverse effects from use of ICS in pregnancy, pregnant women with asthma and their physicians still hesitate to use them. Hodyl and colleagues showed that ICS therapy in pregnant women with asthma did not suppress the glucocorticoid-regulated pathways in the placenta and fetus, providing some reassurance in regard to ICS use in this population (6). A report by O'Byrne and colleagues, who did not detect increased rates of pneumonia by studying 9,067 patients that had participated in 26 double-blind placebo-controlled trials, was also somewhat reassuring (7).

A surprising trial in 2011 suggested that when it comes to asthma treatment, *efficacy* in a clinical trial may not always predict *effectiveness*, because compliance is not monitored and enforced in the real world. ICS are generally regarded as being substantially more effective than leukotriene receptor antagonists. However, in an open-label clinical effectiveness trial performed in primary care practices in the United Kingdom over 2 years of treatment, Price and colleagues found that a leukotriene receptor antagonist was almost as effective as ICS alone, and also as effective as LABA when used as an add-on to ICS, over the short term (8). These surprising outcomes require repetition.

We gained further insight into the use of anti-IgE in 2011. A study in inner-city children showed that anti-IgE therapy improved days without symptoms. However, the salutary effect occurred almost entirely during two seasons of the year. During the remainder of the time, the effect was no different than placebo (9). Interestingly, the maximum improvement in symptoms occurred during the run-in prior to randomization, suggesting strong participation or placebo effects. This interesting observation was reinforced in a study by Wechsler and colleagues, which found that patients' expectations can significantly improve patient-reported outcomes, even in the absence of objective improvement in lung function (10).

Medication choices or administration regimens were not the only interventions shown to affect asthma outcomes. Two articles illustrated the importance of asthma education in this regard. A written action plan upon discharge from an acute care setting increased adherence to prescribed medications in the third and fourth week after the acute episode and improved asthma control in 40% more patients (11). A school-based intervention targeting low-income, urban minority high-school students with group-based and individually tailored teaching sessions, enhanced by "academic detailing" (an educational technique for the adolescent's medical providers) showed significant improvements in asthma control and health care utilization (12).

Lastly, a study in 2011 suggested that we may be getting closer to personalizing asthma pharmacotherapy. Using material from white trios in the Childhood Asthma Management Program, followed by confirmation in additional populations, Tantisira and colleagues identified a polymorphism in the glucocorticoid-induced transcript 1 gene (GLCCI1), which appears to explain 6.6% of variability in improvement in FEV_1 after ICS therapy (13). Although this may be a small degree of variability, it suggests that genomic information may supplement emerging phenotypic and biomarker information to eventually allow us to individualize therapy.

(*Received in original form April 8, 2012; accepted in final form May 14, 2012*)

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Am J Respir Crit Care Med Vol 186, Iss. 1, pp 35–40, Jul 1, 2012

DOI: 10.1164/rccm.201204-0634UP
Internet address: www.atsjournals.org

New Therapies

This was an exciting year for advancing our understanding of interventions targeting specific pathobiologic processes in asthma. Lebrikizumab, a monoclonal antibody that binds to interleukin (IL)-13, was shown to produce a small but statistically significant improvement in mean FEV_1 (5.5%) in individuals with poorly controlled asthma on moderate to high doses of ICS (14). Although this trial was too small to detect a difference in asthma control and exacerbations, the effect on airway caliber confirms a role for IL-13 in the asthmatic process. Of additional interest, levels of periostin, a biomolecule produced by activated epithelial cells, seemed to identify patients who were more likely to experience improvement with lebrikizumab. Whether this treatment will produce further clinically important effects in asthma remains to be determined.

Two years ago, two studies demonstrated that anti–IL-5 therapy might be very effective in patients with persistent sputum eosinophils despite high-dose ICS therapy (15, 16). A study by Castro and colleagues examining the efficacy of reslizumab, an antibody to IL-5, in patients with eosinophilic asthma that is poorly controlled despite high-dose ICS therapy, suggests that we may need to temper our enthusiasm in this regard (17). Despite reductions in sputum and blood eosinophils and 180 ml/second improvement in FEV_1, asthma control was not improved after 15 weeks of treatment, except in subgroups of patients with very high scores on the Asthma Control Questionnaire (ACQ $>$ 2) or history of nasal polyposis. It remains to be determined whether this study was simply too short to detect differences.

PHENOTYPES IN ASTHMA

Severe Asthma

Patients with difficult-to-control asthma may be a particularly heterogeneous group of patients. Their clinical presentation may be related to diverse underlying etiologies and differing complicating factors, and may include alternate biological processes. In 2010, the NHLBI Severe Asthma Research Program investigators identified five clusters of phenotypically distinct individuals with severe asthma by performing an unsupervised cluster analysis (18). Fitzpatrick and colleagues applied similar methods to a cohort of 161 children with severe asthma, which segregated them into four clusters with increasing severity and atopy from cluster 1 to cluster 4 (19). The clusters bore similarities to the adult clusters except that the degree of lung function impairment was less in children. Cluster 1 was characterized by children with late-onset, symptomatic asthma with lower exhaled nitric oxide levels. Cluster 2 consisted of children with early-onset atopic asthma with reversible lung function but high health care utilization. Cluster 3 was similar to cluster 2, except for incompletely reversible lung function and more comorbidity. Children in cluster 4 had the lowest lung function with the greatest symptoms, medication use, and health care utilization. Whether these clusters differ biologically or in response to therapy will need to be determined.

Vocal cord dysfunction is present in 4–10% of patients referred to "difficult asthma" clinics. Low and colleagues performed continuous dynamic computed tomography of the larynx in healthy volunteers to develop and validate an analysis algorithm for quantification of normal vocal cord function (20). They then examined 46 individuals with difficult-to-treat asthma. Excessive narrowing of the vocal cord diameter was observed in 23 of the patients studied. Although this technique provides information about the overall laryngeal function rather than just the vocal cord movement seen upon endoscopy, it is yet to be validated by laryngoscopic confirmation and association with clinical phenotypes and response to therapies.

Esophageal reflux is thought to contribute to poor control in a subset of patients with difficult-to-control asthma. In 2010, Kiljander and coworkers reported a small improvement in lung function in individuals with asthma with symptomatic gastroesophageal reflux disease (GERD) who were treated with esomeprazole (21). In January 2012, a study showed that this benefit did not extend to pediatric patients with asthma *without* GERD symptoms, even in those with documented GERD (22). On the contrary, this study found an increase in upper respiratory infections and bone fractures in the treatment group, suggesting that treating individuals with severe asthma without symptomatic GERD may not be advisable.

Race

There are clear differences in lung function among individuals with asthma in different racial categories. Van Sickle and colleagues found that socioeconomic status also affects FEV_1 (23). They reported that higher education was associated with higher FEV_1 in both males (mean 69.13 ml) and females (mean 50.75 ml). These differences were greater in whites than in blacks. Zhang and coworkers reported that ethnicity also affects lung function (24). Peak expiratory flow rates were lower in Hispanic as compared with non-Hispanic girls diagnosed with asthma, despite adjustment for socioeconomic status. The investigators speculate that their observation may be related to access to care or controller medications, dietary differences, or genetic variation. Further investigations to determine the implications of racial and ethnic differences on lung function are warranted to identify potentially preventable causes.

Particular Biological or Risk Phenotypes

Novel biomarkers are being sought in an effort to understand the biological risk that puts individuals with asthma at risk for certain phenotypes. An unsupervised analysis of peripheral blood proteins revealed a panel of four biomarkers associated with iron metabolism pathways and acute phase response that showed the ability to identify individuals with asthma from healthy controls and those with chronic obstructive lung disease (25). After adjustment for body mass index and other confounders in a study of 18,000 children from farming communities in rural West Virginia, Cottrell and colleagues demonstrated that metabolic derangements in obesity such as acanthosis nigricans and elevated triglycerides were associated with increased asthma prevalence (26). The causal pathways for these associations remain to be determined.

Proteomic analysis of bronchoalveolar lavage fluid of individuals with asthma identified increased concentrations of a group-specific component protein (Gc) when compared with fluid from controls (27). This protein is expressed on alveolar macrophages and epithelial cells, and can induce inflammation by its ability to bind with vitamin D metabolites. Neutralization of the Gc protein leads to significant improvements in airway hyperresponsiveness and inflammatory cell recruitment in an experimental mouse model, suggesting it may play a role in the development of asthma in humans.

The extent to which prenatal or early life factors determine the predilection to develop asthma was also addressed by several studies in 2011. Data from Turner and colleagues suggest that decreased fetal size is a determinant of lung function and risk of asthma in childhood (28). For each millimeter increase in fetal size in the first trimester, the risk for asthma decreased by 6% and FEV_1 increased by 6 ml at age 10 years. Persistent slow growth in the second trimester was also associated with asthma risk. Camargo and colleagues found that cord-blood vitamin D levels were inversely associated with risk of developing respiratory infection and wheeze in childhood (29). Gupta and

colleagues found an inverse relationship between serum vitamin D levels in young children with severe asthma and their airway smooth muscle mass (30). Another interesting report by Macsali and colleagues found that menarche at the age of 10 years or earlier compared with menarche at age 13 years was associated with lower lung function and more asthma symptoms (31).

Exacerbations

The biology of asthma exacerbations may not be identical to processes that play an etiological role in asthma itself. Two articles in the *Journal* shed light on the pathobiology of asthma exacerbations. Denlinger and colleagues reported that half of the asthma exacerbations in a group of 52 adults with asthma were associated with human rhinovirus infection, with infections of minor group A human rhinovirus infections being 4.4-fold more likely to cause exacerbations (32). Innes and coworkers shed further light on the pathobiology of exacerbations by showing that patients who were more susceptible to asthma exacerbations were 2.3 to 5.8 times more likely to possess the histoblood group O-secretor mucin glycan phenotype (33). Intriguingly, expression of O antigen at mucosal epithelial surfaces in the gut has been shown to confer risk for specific viral diarrheas, suggesting a tie-in to the viral work of Denlinger and coworkers (34).

PATHOBIOLOGICAL MECHANISMS IN ASTHMA

Articles in the *Journal* and elsewhere continued to examine the contribution of cellular constituents, cytokine and mediator pathways, and environmental exposures to the development of asthma.

Eosinophils

Eosinophils are strongly associated with asthma and a subset of severe asthma. Data suggest that eosinophil activation may be of some importance very early in life, before the development of atopy-related symptoms. Elevated levels of eosinophil protein X in urine of 1-month-old high-risk neonates showed a strong association with development of allergic sensitization, nasal eosinophilia, and eczema by the time they were 5 years old (35).

Whether or not eosinophils contribute to the long-term effects on the airway anatomy is controversial. Broekema and colleagues found that airway remodeling due to eosinophil activation distinguished patients with current asthma from patients with complete remission of the disease (36). In contrast, Fattouh and coworkers found negligible effects of allergen challenges on subepithelial collagen deposition and smooth muscle thickening in eosinophil-deficient house dust mite–induced allergic animal models (37).

Mast Cells

Mast cells are thought to play a role in the pathobiology of asthma. Balzar and colleagues showed that a particular type of mast cell, that is both tryptase and chymase positive, is more abundant in the airway walls of patients with more severe asthma and is associated with increased bronchoalveolar lavage levels of prostaglandin (PG)D_2 (38). Kearley and coworkers, using anti–IL-9 in a chronic allergen mouse model, suggested that IL-9 may play a role in homing of mast cells to the lung and their expression of profibrotic mediators (39). An accompanying editorial pointed out that the direction of the effect of IL-9 is very stimulus dependent because IL-9 may play a protective role in injury-induced fibrosis (40).

The importance of a particular phenotype of mast cells, and related inflammatory cells–basophils, was highlighted by a study examining specific IgE in sputum (41). The authors reported that despite the fact that dust mite–specific antigen was equally elevated in the sputum of individuals with "intrinsic" asthma and in individuals with "atopic" asthma, the former did not react to allergen inhalation challenge. As pointed out by the editorialists, what distinguished these subjects from each other was the ability of blood basophils from the atopic donors to be stimulated by the sputum IgE (42). Thus, the difference may lie in differential thresholds for activation of the inflammatory effector cells.

Dendritic Cells and Environmental Interactions

As discussed in last year's review, the role of dendritic cells in controlling TH2-type inflammation has gained increasing interest (2). In 2011, a mouse model of dendritic cell–induced Th2-type inflammation suggested that dendritic cells played a role in subsequent neo-allergen Th2-skewed inflammation that could occur in the absence of adjuvant (43). As pointed out in the accompanying editorial, these data suggested that the effect of these dendritic cells could persist even after inflammation had resolved and might explain the progression of sensitization that accompanies asthma and eczema (44).

Interest in the dendritic cells' role in Th2-type inflammation led to investigations of interventions. A pair of studies in murine allergen models suggested that thrombomodulin and a phycocyanin derived from seaweed (used in herbal remedies) could inhibit allergen-induced responses through their effects on dendritic cells (45, 46). The former compound appears to induce tolerogenic dendritic cells, and the latter elicits IL-12 p70 production.

Studies published in 2011 also suggested that dendritic cells may play a role in the reported relationship between an increase in diversity of microbial exposure and decreased risk of development of asthma (47). Herbst and colleagues reported that in germ-free mice, recolonization with commensal flora decreased the inflammatory response to allergen (48). Although the regulatory T-cell populations of the germ-free mice were unaltered, these animals had increased basophils and reduced macrophages and plasmacytoid dendritic cells. These data suggest that commensal microbiota are important in dendritic cell development and maintenance of immunologic tolerance (49).

Cytokines and Mediators

The role of IL-13 in asthma pathobiology continued to be a major focus of interest. Ingram and colleagues provided further insight into how IL-13 might transduce its effects by demonstrating that IL-13 stimulates airway fibroblast invasion in asthma and that this mechanism depended on matrix metalloproteinases and transforming growth factor β (TGF-β) (50). Gauvreau and colleagues demonstrated that anti–IL-13 could partially inhibit the late-phase bronchospastic response to allergen inhalation in humans but not the increase in airway responsiveness or airway eosinophils (51). As pointed out by the editorialists, the isolated response left us wondering whether anti–IL-13–based therapies would be clinically useful and whether there would be particular patient groups that would benefit (52). However, a subsequent publication in 2011 (14) using an anti–IL-13 antibody in humans targeting patients with elevated periostin levels showed an 8.2% greater improvement in FEV_1 than similar patients treated with placebo. These data suggest that anti–IL-13 therapy may actually be useful in the clinical treatment of asthma and that there may be biological markers to identify those most likely to respond.

There has also been increasing interest in IL-17 and Th-17's role in asthma. In a murine allergic inflammation model, Li and colleagues showed that Th17 cell differentiation is dependent on autocrine signaling through prostaglandins (53). More specifically, they showed that the autocrine production of $PGF_{2\alpha}$ and PGI_2 is dependent on cyclooxygenase-2–induced synthesis

and activation of respective receptors on the Th-17 cells. As pointed out in an editorial, an attractive possibility for the role of Th-17–induced inflammation might be the so-called "Th2-low" asthma phenotype associated with non–steroid-responsive disease (54). However, a report by Besnard and colleagues demonstrates that the Th17 story may be even more complex, because Th17 cytokine effects may vary temporally (55). They showed that the Th17-derived cytokine, IL-22, is elevated in the serum of patients with asthma and is critical to the development of allergic sensitization in the murine model. However, IL-22 administration *during* allergen challenge *protects* against lung inflammation potentially through down-regulation of IL-17A. In this regard, late in 2010, Wang and colleagues identified a novel subset of $CD4^+$ memory effector cells that produce IL-17 that are elevated in the circulation of patients with asthma (56).

TGF-β stimulates the development of Th17 cells, explaining a possible role for this biomolecule in asthma. An additional mechanistic insight for the potential role of TGF-β in asthma was elucidated in 2011 by Michaeloudes and colleagues (57). They showed that nuclear factor E2–related factor 2, which is suppressed by TGF-β, up-regulates antioxidant genes and reduces airway smooth muscle proliferation and that control of these genes was altered in severe asthma. In relationship to antioxidant activity and asthma, Kim and colleagues reported that a novel antioxidant (CB3) could increase glutathione levels in a murine allergen provocation model and decrease the inflammatory response in association with decreased p38 mitogen-activated protein kinase phosphorylation (58).

Environmental Risk

Exposure to chlorine in swimming pools has frequently been associated with asthma symptoms in children. Font-Ribera and colleagues reported that they did not find an association between swimming pool attendance in infancy and childhood and asthma symptoms, atopy, or bronchial hyperresponsiveness between the ages of 7 and 10 in 5,738 British children (59). However, an editorialist opined that the reported study may have been confounded by physical activity, selection bias, lack of data after the age of 10 years, and underestimation of exposure (60).

Acetaminophen use depletes the antioxidant glutathione S-transferase in the airways (61). The ISAAC (International Study of Asthma and Allergies in Childhood) investigators found that asthma risk increased to 2.5-fold if acetaminophen was used more than once a month in children (62). Another birth cohort study reported that acetaminophen use in the first year of life was associated with a dose-dependent increase (up to sevenfold) in incident wheeze at age 3 years (63). Although these data are of significant interest, they are based on retrospective observations and require validation in well-designed prospective clinical trials before advocating changes in current prescribing recommendations for analgesics.

Remodeling

In 2010, several articles in the *Journal* suggested a role for vascular remodeling in the pathobiology of asthma (64). This line of reasoning gained further support in 2011. A study of patients with asthma who developed late-phase allergen responses found a substantial increase in endothelial progenitor cells in their sputum (65). Increased number and diameter of blood vessels in endobronchial biopsies were also observed after challenge. Another group of investigators showed that repeated bronchoconstriction via methacholine produced structural changes in the airways similar to allergen challenge, suggesting that repeated epithelial stress is an independent contributor to airway remodeling (66). In regard to the effect of allergen in the airways, a group of investigators suggested that disruption of the structure of surfactant protein D after allergen challenge was associated with an increased inflammatory response to the allergen (67).

Nitric Oxide and the Airways

The effects of pathways that modulate nitric oxide (NO) synthesis were of interest in 2010 (68, 69) and continue to be areas of active exploration. Arginase competes with NO synthase (NOS) and thus alters NO production. Investigators in 2011 showed that DNA methylation of the arginase2 gene was inversely correlated with exhaled NO in children (70). Correspondingly, another article reported that common regulatory haplotypes of arginase1 were associated with altered bronchodilator response (71). The precise mechanism by which NO synthesis affects β-agonist responses remains unclear. Intriguingly, another work indirectly suggested that NOS inhibition might lead to increased airway reactivity in asthma. These investigators showed that asymmetric dimethylarginine, a NOS inhibitor, was increased in human asthma and asymmetric dimethylarginine administration increased airway responsiveness in naive mice (72). Lastly, Ritz and colleagues suggested that endogenous cortisol induced by stress might modulate NO production (73).

Miscellaneous Mechanisms

A report by Vieira and colleagues raised the possibility that yet another receptor system may play a role in modulating asthmatic allergic airway inflammation (74). Purinergic receptors are expressed on cells of the hematopoietic system, including eosinophils, dendritic cells, and T cells. The authors demonstrated that inhibition or ablation of the purinergic receptor P2Y6R reduced murine allergic lung inflammation (in which epithelial P2Y6R was shown to be strongly up-regulated) and that this reduced inflammation was associated with decreased epithelial IL-6 and IL-8 levels. Of note, a genome-wide association study reported by Ferreira and colleagues found that a variant in the IL-6 receptor (IL6R) increased the odds ratio for asthma to about 1.1 (75). The association with variant in the IL6R gene raises the possibility of examining the effectiveness of tocilizumab (an IL6R antagonist used in rheumatoid arthritis) in the treatment of asthma in a genotype-dependent manner.

CONCLUSIONS

This was the year for "splitters" as opposed to "lumpers" in thinking about asthma. Work in 2011 suggested that not all individuals with asthma share the same biological underpinnings. The ability to understand and identify particular "endotypes," combined with the development of therapies that target very specific pathways, appears to be moving us in a direction of targeted and biomarker-driven therapy. Our advance in the understanding of basic pathobiological mechanisms underlying the disease will help accelerate this process.

Author disclosures are available with the text of this article at www.atsjournals.org.

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