Published in final edited form as:
J Allergy Clin Immunol. 2010 January ; 125(1): 79–84. doi:10.1016/j.jaci.2009.11.028.

Advances in Adult Asthma Diagnosis & Treatment in 2009

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Abstract

There is a growing need to standardize and validate outcomes for asthma research. In this review of asthma-related publications from the Journal in 2009, efforts to standardize methodology and reporting of translational research, the influence of the environment, therapeutics, and management of asthma are highlighted.

Keywords

asthma; adults; genetics; inhaled corticosteroids; nitric oxide; health disparities; biomarker; leukotriene modifier; obesity

INTRODUCTION

As in past Advances,[1-7] our review examines research on management, therapeutics, and the role of environmental exposures on asthma. During the past year substantial efforts were initiated to promote standardization and validation of outcomes employed in asthma–related research. In July 2009 a joint task force of the European Respiratory Society and the American Thoracic Society published recommendations providing the foundation for standardization of endpoints for both clinical trials and practice.[8] Specifically, the Task Force sought to define asthma control, which they considered a "summary term,"[8] exacerbations, and severity. Their recommendations included a multi-component assessment of control. A consortium of several NIH Institutes, the Agency for Healthcare Research and Quality, and the Merck Childhood Asthma Network will hold an Asthma Outcomes Workshop in March, 2010 to further refine standard definitions and data collection methodologies and identify promising new outcome measures. The Workshop's goals are to enable comparisons across studies and clinical trials and to enhance the level of confidence in research findings. This consortium will consider endorsing a selective set of "core" outcomes to be identified as required outcome measures in NIH-initiated asthma clinical research programs. Also over the past year, the National Committee for Quality Assurance and the American Medical Association Physician Consortium for Performance Improvement have proposed asthma measures to be used in assessing quality improvement.[9]

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Outcomes, whether used for research, patient care decisions, or quality improvement, must be valid, easily obtainable, and reproducible. Some like self-report measures, e.g. questionnaires and unobserved effort-dependent peak flow records, are easy to obtain, but may not be valid or reproducible. Nevertheless, they may add another dimension when combined in an multi-component assessment.[8] As we review this year's research, we invite you to consider the study populations, their applicability to our own patients, and the measures used for outcomes.

GENETICS: FROM BENCH TO BEDSIDE

Several genetics studies suggest possible therapeutic applications. Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine that induces myeloid dendritic cells to stimulate naïve T-cells to differentiate into TH2 cells.[10] *TSLP* is located on chromosome 5q22 near genes for IL-4, IL-5, IL-9, and IL-13. He et al,[11] using DNA from 5565 individuals from 4 asthma studies, identified *TSLP* variants associated with asthma, mostly defined as self-reported doctor's diagnosis.

Barton et al[12] studied urokinase plasminogen activator receptor, *PLAUR*, as an asthma susceptibility gene, in United Kingdom (UK) and Dutch families by combining several studies with slightly different inclusion criteria. Using linkage and association analyses, they found *PLAUR* associated with decline in FEV1 and bronchial hyper-responsiveness to methacholine or histamine.

Haller et al[13] compared rare variants of the *IL4* gene in subjects of African descent. They hypothesized that because populations of African descent have increased genetic variation, rare variants of a gene important in atopic disease like *IL4* might play a role in asthma susceptibility. African Americans with doctor-diagnosed asthma and demonstrated bronchial hyperresponsiveness to methacholine or reversibility of obstruction with albuterol were compared to African Americans without asthma. They identified 26 private SNPs in the *IL4* region: 18 present only in cases and 8 only in controls. The investigators concluded that these rare variants, most not included in common genotyping platforms, may contribute to asthma susceptibility in African American subjects.

Basu et al[14] found the Arg16 genotype of the adrenergic β_2-receptor agonist gene, *ADRB2*, increased the risk of asthma exacerbations among young patients using daily β_2-agonists. By recruiting additional subjects to those enrolled in an earlier study, they doubled the study population from 546 to 1190. These studies of genetic risk factors demonstrate tradeoffs of increasing sample size by combining patient populations with potential changes to generalizability and potential limitation to the measures that can be used to characterize asthma and study outcomes.

MEASURING OUTCOMES AND QUALITY OF CARE

Clinical measures

The effort to standardize outcomes has led to examination of self-report questionnaires and biomarkers. Schatz et al[15] determined the minimal clinically important difference on Asthma Control Test (ACT).[16] Four large samples were recruited: 1) subjects from an internet comparison study of modes of administration of surveys, 2) patients from 6 asthma specialty practices, 3) asthmatic individuals recruited from local media advertising or by consulting one of these advertising practices and 4) subjects from the Kaiser Permanente asthma database. When applying ACT results, users must consider how representative these patients are to theirs.

Yong and Werner[17] identified Medicaid beneficiaries from the Healthcare Effectiveness Data and Information Set (HEDIS) in order to evaluate the HEDIS quality measure for asthma care used by health plans. Subjects satisfied at least one asthma-related category in both 2001 and 2002: emergency department (ED) visit, hospitalization, at least 4 outpatient visits and at least 2 asthma-medication dispensing events, or at least 4 asthma medication-dispensing events. The investigators compared: 1) the current HEDIS criterion of at least 1 controller-medication filling, 2) at least 4 controller-medications fillings yearly, and 3) a controller-to-total asthma medication ratio of at least 0.5. Filling 1 or 4 asthma controller prescriptions was associated with higher likelihood of exacerbations (ED visit, hospitalization, or dispensing of an oral steroid for asthma), but those with a controller-to-total asthma medication ratio of at least 50% were 23% less likely to have such an exacerbation. The authors concluded that the controller-to-total asthma medication ratio is more sensitive to unmeasured disease severity. These findings are particularly pertinent as HEDIS criteria are now under revision.

Biomarkers

Biomarkers potentially can noninvasively assess airway inflammation, complementing clinical measures. FENO, described in last year's Advances as an indicator of eosinophilic inflammation,[4] may be influenced by non-pathologic factors such as genetic and environmental variation.[18] Information on its limitations grows. Smith et al[19] found reduction of FENO levels when prednisone was administered to adults with mild-to-moderate asthma, but the levels did not always agree with values predicted by published references, nor did they predict good control with inhaled corticosteroids (ICS). The authors found “personal best” FENO may be a better marker than absolute levels, but whether FENO is more feasible and cost-effective than patient history or spirometry is doubtful.[20] Gruchalla et al[21] examined inner-city asthmatic adolescents, for biomarkers and other predictors of exacerbations. FENO was not predictive of maximum symptom days recalled over a two-week period and only weakly correlated with exacerbations. Additionally, all the baseline subject characteristics accounted for only about 12% of the variance for future maximum symptom days. The authors concluded the usual predictors of disease activity have little predictive power in a population already receiving guidelines-based care. This underlines the importance of investigation of outcomes presented above.[8]

Gergen et al[22] examined total IgE as a potential biomarker of cumulative sensitivity to all allergens. Using National Health and Nutrition Examination Survey (NHANES) data, they found IgE varied with age, sex, race/ethnicity, serum cotinine level, body size, and socioeconomic status and was associated only with self-reported asthma among persons with positive allergen-specific IgE. Thus, measurement of total IgE was not recommended. Kaminska et al[23] searched for biomarkers that distinguish reversible from irreversible obstruction in severe asthma. None of the biomarkers of inflammation or remodeling (e.g., eosinophil cationic protein (ECP), myeloperoxidase, matrix metalloproteinase analyses, cytokines, cell counts) separated these two groups. Wu et al[24] examined the repeatability of various biomarkers over 4 years in the Childhood Asthma Management Program. They found FEV1 and PC20 but not bronchodilator response had high repeatability.

The mannitol bronchoprovocation test (MBT) is an indirect test, acting on smooth muscle by stimulating mediator release, while methacholine and histamine directly cause muscle contraction. Sverrild et al[25] determined the sensitivity and specificity of MBT in young adults, independently classified as asthmatic, as 58.8% and 98.4% respectively. Thus, MBT may have greater specificity, but less sensitivity than bronchoprovocation by methacholine or histamine. There is a tradeoff between sensitivity and specificity.[26] Sensitive tests are more likely to generate false positives and have fewer false negatives, while specific tests are more likely to have false negatives and fewer false positives. Specific tests, like MBT,

are best used to diagnose asthma, while methacholine and histamine bronchoprovocations are best used to rule out asthma.

ENVIRONMENT

Pollution, viral infection, and social stress are some environmental risk factors studied in 2009. Traffic exposure has been associated with adverse outcomes in asthmatic children.[27, 28] In adults, Balmes et al[29] found FEV1 positively associated with distance from nearest roadways. Controlling for income, itself related to distance from major roadways, did not substantively change this association. The study was a secondary analysis and limited by non-uniform inclusion criteria as some subjects had rhinitis rather than asthma.

Ozone increases the risk of asthma in part by exposing lung tissue to higher oxidative stress. Glutathione-S-transferase is an antioxidant. Deletion of an allele of the glutathione-S-transferase M1 (*GSTM1*) gene produces a nonfunctioning product associated with asthma and poorer lung function. Alexis et al[30] compared the effects of ozone exposure in healthy volunteers with the wildtype and null *GSTM1* genotypes. *GSTM1* null volunteers had increased neutrophil and activated macrophage counts in induced sputum 24 hours after ozone exposure, consistent with the lag time to symptoms previously observed with ambient ozone exposure. There was no difference in FEV1 and FVC between groups, although values decreased in both groups after ozone exposure.

Respiratory viral infections also increase the risk of asthma exacerbations. De More et al[31] hypothesized that defective host defense against viruses is defective in asthma. Young adults with or without mild allergic asthma were inoculated nasally with rhinovirus. No difference was observed in cold symptoms or viral shedding in nasal lavage and sputum samples. With the exception of sputum eosinophil counts, which were higher at baseline in allergic asthmatic subjects, there were no differences in cytokine or cellular composition of the samples. The study hypothesis was not supported, although the sample size was small.

Sternthal et al,[32] probed the effect of maternal lifetime interpersonal trauma (IPT) on the fetal TH2 cytokine/chemokine milieu in a cohort of Boston-area inner-city women during and after pregnancy. Their secondary analysis assessed and correlated stress at successive life stages (childhood, adolescence, adulthood before and during the current pregnancy), and found an association of chronic maternal IPT with higher cord blood IgE. While preliminary, the study emphasizes the need for better understanding of lifetime maternal stress on asthma outcomes in infants.

PRACTICE or MANAGEMENT

Therapeutics

Leukotriene modifiers—The possible association of montelukast with depression was raised by the FDA in 2007. In 2008 Holbrook and Harik-Khan[33] combined data from three studies and found no association. In 2009, responding to FDA requests, the manufacturers performed secondary analyses of studies comparing montelukast with placebo or comparison drug.[34, 35] Few behavior-related adverse events (e.g. depressive symptoms, anxiety, agitation, aggression)[34] and no reports of completed suicide were found.[35] Although reassuring, as Kelsey notes in an accompanying editorial, patients with significant mental health disorders are frequently excluded from clinical trials.[36]

Hope et al[37] studied oral aspirin challenges in aspirin-exacerbated respiratory disease in order to better understand risk factors for challenge-induced adverse events. Moderate-to-severe bronchial reactions were more likely when the baseline FEV1 was less than 80%,

leukotriene modifier premedication was not used, and there was a history of asthma-related ED visits. Most reactions occurred in the 45-100 mg dose range.

Wise et al[38] and the American Lung Association Asthma Clinical Research Centers examined the effect of drug presentation on asthma outcomes in adults with poorly controlled physician-diagnosed asthma. The study used a factorial design and randomized subjects to montelukast or placebo and a neutral or optimistic ("enhanced") message about the benefit of treatment. Asthma control improved in the placebo-treated, but not montelukast-treated recipients of enhanced messaging. Peak flow and other lung function measures were not associated with message assignment, emphasizing that reported symptoms and lung function measurement do not always coincide; both should be included in reports of clinical research.

Inhaled Corticosteroids—Thomas et al[41] examined whether the first increase in medication for patients already prescribed a low-dose ICS should be increased ICS or the addition of a long-acting beta-agonist (LABA). Patient cohorts were selected from the General Practitioners Research Database, a large UK electronic medical record database. Symptom control with high dose ICS was not as effective as adding a LABA, but higher dose ICS alone was associated with a lower risk of severe exacerbations and hospitalizations. However, the baseline characteristics of the two groups were dissimilar in several important parameters e.g., the ICS cohort was younger with lower BMI, fewer had required oral steroids in the previous year, and more had had respiratory hospitalizations during the year prior to enrollment.

Pavord et al[42] conducted a 52-week parallel-group, randomized, double-blind study comparing high dose budesonide /formoterol (BF) (800/12 mcg) twice daily plus as needed BF to low dose BF(200/6 mcg) twice daily plus as-needed inhaled terbutaline. Eosinophil counts from sputum and bronchial biopsy (week 0 and 52) were lower in the higher dose BF-group, but there was no difference in other inflammatory biomarkers (FENO, mast cell numbers, ECP, or lymphocytes), clinical exacerbations, or FEV1. At entry subjects were using ICS, approximately 800 mcg/d. Although control was not measured, the findings suggest ICS doses can be reduced in comparable patients.

Haahtela et al[43] studied whether early ICS therapy had lasting benefit, re-examining 90/103 patients who 13 years earlier experienced new-onset mild asthma and were randomized to the immediate start of ICS versus a one-year delay.[44] At year three, patients immediately treated with the ICS had better asthma outcomes, but in the current re-analysis, all subjects had normal lung function and there were no differences in clinical or functional variables. Thus, it remains unclear whether early ICS therapy makes a long-term difference.

Folate—Because folic acid has been associated with inflammatory diseases, Matsui and Matsui[45] examined a potential role for folate in either mitigating or promoting allergic diseases. Using NHANES data, they found folate levels were inversely associated with total IgE levels, atopy, and wheeze, but further interpretation was precluded by the study design.

Practice

Within the ED—Tsai et al[46] conducted a retrospective chart review of quality of care of acute asthma in 63 EDs, using National Emergency Department Safety Study data. They found the overall concordance of treatment with National Asthma Education and Prevention Program Guidelines[47-49] was moderate and associated with reduced risk of hospitalization, although there was geographic variation.

Women's Health—Whether sex hormones affect asthma risk is unknown. Macsali et al[50] used postcards to survey Northern European women for report of doctor-diagnosed asthma and the use of oral contraceptives. Among responders, asthma was associated with oral contraceptive use by normal-weight and overweight but not lean women. The cross-sectional study design did not permit analysis of temporal associations and explanatory relationships, and selection bias may have influenced the results.

Several studies found poorer asthma outcomes in women. Temprano and Mannino[51] analyzed data from the National Asthma Survey, Four State Sample (Alabama, California, Illinois, Texas). Women were more likely to have poorer asthma control as reflected by several self-reported short-term and long-term variables including asthma hospitalization, consistent with other national survey data.[52] Interestingly, twice as many women as men responded to the Survey. Appleton et al,[53] followed a large Australian cohort for a mean of 3.5-years, and found incident self-reported cardiovascular disease is associated with asthma particularly in females (OR 3.24 [95% CI: 1.55-6.78]).

How asthma affects pregnancy remains a concern. Cookson et al[54] conducted a longitudinal secondary analysis from a UK birth cohort. Higher levels of maternal anxiety during pregnancy increased the child's risk of asthma at 7.5 years. Blais et al,[55] merged 3 Canadian administrative databases to examine the association of congenital malformations with ICS use by asthmatic women during the first trimester of pregnancy. There was no increase in congenital malformations among offspring of 4392 women who used ICS less than 1000 mcg/day versus control asthmatic women who did not use ICS during the first trimester. However, there was an increased risk of congenital malformation, but not of major malformations, in the 154 women who used more than 1000 mcg/day compared with the 4392 women using less ICS (RR 1.63[95%CI: 1.02-2.60]). Residual confounding by severity of asthma was possible: women on higher doses of ICS had more severe asthma; their asthma severity rather than its treatment may be the primary association.

Asthma and obesity—It remains controversial whether excess body mass and asthma are related by pathophysiology or share other environmental, behavioral, and social risk factors.[56] Marcon et al[57] examined the 4-year change in weight and FEV1 in European adults with asthma and found BMI gain associated with a decline in FEV1, but only for subjects without measurable airflow obstruction at baseline, suggesting the importance of weight management early in asthma. Interestingly, in a cross-sectional study Clerisme-Beaty et al[56] found no association of asthma control with obesity in US urban patients. However, in a 9-year prospective study of African American women, Coogan al[58] observed higher BMI associated with increased risk of self-reported physician-diagnosed asthma in a dose-response relationship. Sutherland et al,[59] found increased BMI was not associated with clinically significant worsening of asthma impairment, using data from 1265 participants with mild-to-moderate asthma from Asthma Clinical Research Network studies. With differences in methodology, study populations, and study outcomes, whether asthma is physiologically associated with obesity remains unproven. As the authors admit, these studies are open to detection bias. Standardized and validated measures of asthma impairment are particularly needed here. Studies of well-characterized asthmatic patients with elevated BMIs who undergo weight loss will be of great interest.

Asthma and sleep apnea—Julien[60] found obstructive sleep apnea (OSA) more prevalent in patients with severe asthma. The basis for this relationship is not elucidated. However, OSA-hypopnea severity measures did not correlate with asthma severity or control scores, including FEV1.

Adherence—Janson et al[61] conducted a 24-week prospective randomized controlled trial to improve adherence to ICS and asthma control in 95 adults with moderate or severe asthma. The intervention, comprised 3 30-minute sessions delivered by a certified asthma educator, and included facts about asthma, medications, spirometry, peak flow, use of inhalers and allergen skin testing tailored to the patient. Control asthmatics performed self-monitoring, but did not receive asthma education. Mean adherence did not significantly differ between groups but a relative decrease in perceived symptoms and nighttime awakenings occurred in the intervention group. Morning peak flow and FEV1 improved equally in both groups. Mean adherence did not differ, but the usual decrease over time was attenuated in both groups. Cost-effectiveness of an asthma educator was not calculated. This important study shows that focusing attention on patients' asthma and not necessarily this specific intervention improves outcomes.

Naimi et al[62] studied adherence to prescribed ICS in 40 older urban adolescents. Electronic monitoring was combined with semi-structured face-to-face interviews, conducted at the beginning and end of the one-month observation period. The interviews explored teens' attitudes toward ICS treatment and their suggestions for improving adherence. Forty-three percent had an ED visit and 20% a hospitalization for asthma in the past year. Despite knowing ICS use was monitored, teens took an average 43% (range: 4%-89%) of their prescribed doses. They disliked ICS's taste, doubted the necessity of taking it regularly, and thus forgot to do so when feeling well. Although most felt well, there was significant variation in FEV1: mean 98% predicted (range 67% to 127%). They expressed annoyance with receiving reminders from parents but saw these reminders as signs of attention and concern. Lives were busy and schedules complicated.

Health equity—The June 2009 issue was devoted to promoting health equity;[63-66] disparities are pervasive in the United States and prominent in asthma. In comprehensive reviews,[63-65] the authors advocated interventions at many levels, e.g, patient-provider interface, practice, health system, community, and nation to improve communication with patients, remove barriers to access, and eliminate the effects of poverty, such as increased exposure to pollution[29] and inadequate schools. Because low literacy is widespread, affecting half of the US population,[67] provider level attention to improving effective health literacy, may be one intervention, leading to better patient-provider communication, patient self-management of chronic diseases, and health outcomes.[68, 69] Adams et al[70] examined the association of asthma with literacy assessed from reading nutrition labels.[71] While low literacy was not more common among those with self-reported asthma, those with low literacy were more likely to report nighttime awakening or hospitalizations. In another study, low literacy was not an impediment to learning skills for self-management.[72]

Esteban et al[73] in a cross-sectional study compared asthma control in 7-15 year-old Island Puerto Ricans (IPR) with Rhode Island Puerto Ricans (RIPR), Dominicans, and whites. Self-reported asthma was milder among IPR compared with RIPRs, but IPRs had more ED visits. These differences may be related to a variety of social (poverty, acculturation, cultural differences in reporting experiences, access to health care) and physical environmental differences, which merit further research including intervention studies. Martin et al[74] tested a community-based intervention to improve asthma control directed at improving self-efficacy for self-management. Of 107 participants with poorly controlled asthma identified from clinics serving low-income African American communities, 42 enrolled. They were randomized to 4 group educational sessions led by a community social worker and 6 home visits conducted by community health workers compared with receiving mailed asthma educational materials. Although only 20% attended all the group sessions and the mean number of home visits was 4, self-efficacy and asthma-related quality of life improved in the intervention group. However, there were no significant changes in clinical outcomes. The

biggest limitation of the study was small size, complicated by the fact the groups differed in educational attainment and household income. This study demonstrates how difficult it is to conduct these needed intervention studies.

Poverty, whether urban or rural, greatly affects asthma and other health outcomes.[63-65, 75] In a cross-sectional analysis Gupta et al[75] found positive community factors such as greater potential for economic development; more sociodemographic diversity, voters, restaurants, and cultural/entertainment facilities have an inverse relationship with asthma prevalence. This relationship was attenuated but not eliminated when controlling for race, suggesting that race serves as a "proxy for many socio-cultural and environmental risk factors for asthma."[75]

CONCLUSIONS

Clinical research is difficult to carry out, but it is evident such asthma research is making important contributions to patient care. Finding ways to recruit adequate and representative patient cohorts and defining outcomes that are standardized and comparable across studies is particularly difficult. We look forward to reporting the results of the current standardization efforts and the results of the Asthma Outcome Workshop along with the significant research conducted in the next year.

Acknowledgments

I gratefully thank Anita T. Gewurz MD and Penny Apter for careful reviews and insightful suggestions.

ABBREVIATIONS USED

ACT	Asthma Control Test
B/F	budesonide /formoterol
BMI	body mass index
CVD	cardiovascular disease
ECP	eosinophil cationic protein
ED	emergency department
EPR3	National Asthma Education and Prevention Program Expert Panel Report 3
FDA	Food and Drug Administration
FENO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in 1 second, percent predicted
FVC	forced vital capacity, percent predicted
GSTM1	Glutathione-S-transferase Mu 1
HEDIS	Healthcare Effectiveness Data and Information Set
ICS	inhaled corticosteroids
IPT	interpersonal trauma
LABA	long acting β-agonist
MBT	mannitol bronchoprovocation test
NHANES	National Health and Nutrition Examination Survey

PLAUR	urokinase plasminogen activator receptor
SNP	single nucleotide polymorphism
UK	United Kingdom

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Table 1

Key Findings in the Care of Adults with Asthma in 2009

• There is an ongoing effort to promote standardization and validation of outcomes for asthma–related research.[38, 63-66]
• The TSLP gene is associated with self-reported doctor-diagnosed asthma[11]
• The current HEDIS criterion of asthma quality of care (at least 1 controller-medication filling) is less predictive of a good clinical outcome than a controller-to-total asthma medication ratio of at least 50%[17]
• Inhaled mannitol is a diagnostic test with high specificity and is best used to diagnose asthma, while methacholine and histamine bronchoprovocation tests are best used to rule out asthma[25]
• FENO was not predictive of maximum symptom days reported by adolescents[21]
• Total IgE was associated only with self-reported asthma among persons with positive allergen specific IgE and has no role as a biomarker for asthma in the general population[22]
• The placebo effect has its greatest influence on self-reported outcomes rather than measures of lung function[38]
• Achieving health equity will require interventions at many levels with attention to patient and provider beliefs, patient-provider communication, social and financial barriers to access, and patient poverty[38, 63-66]