

Achieving asthma control in the inner city: Do the National Institutes of Health Asthma Guidelines really work?

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List of Design Committee Members: *Authors:* Stanley J. Szefer, MD, Peter J. Gergen, MD, MPH, Herman Mitchell, PhD, and Wayne Morgan, MD

Activity Objectives

1. To understand the new concepts introduced in the 2007 asthma guidelines.

2. To identify certain populations at risk for asthma.
3. To appreciate the components of an integrated multidisciplinary approach to asthma management in inner-city children.
4. To understand the barriers clinicians face in implementing National Institutes of Health (NIH) guidelines for treating inner-city children with asthma.
5. To understand the clinical implications of the observations from the Asthma Control Evaluation (ACE) Study and needs for future studies to advance asthma care.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: S. J. Szefer is a consultant for GlaxoSmithKline, Genentech, Merck, Boehringer-Ingelheim, Novartis, Schering Plough; and has received research support from the NIH/NHLBI Childhood Management Program (CAMP), NHLBI Childhood Asthma Research and Education (CARE), NIH/NHLBI Asthma Clin Res Network (ACRN), NIH/NIAID Inner City Asthma Consortium (ICAC), GlaxoSmithKline, NJH.NHLBI Asthma Net, and NEEHS/EPA Childhood Environmental Health Center grant. P. J. Gergen declares he has no conflicts of interest. H. Mitchell has received research support from the NIH/NIAID. W. Morgan is a consultant, and is Chair for the Data Safety Monitoring Board for the Cystic Fibrosis Foundation; is a consultant and is Chair for the North American Scientific Advisory Group for the Epidemiologic Study of Cystic Fibrosis for Genentech; is a consultant for Novartis; and has received research support from the NIH/University of Wisconsin and Novartis.

For children living in inner cities, asthma tends to be more frequent and severe. To characterize, understand, and treat children with asthma living in the inner city more effectively, the National Institute of Allergy and Infectious Diseases established an Inner-City Asthma Program in 1991. In addition, the revised National Asthma Education and Prevention Program Expert Panel 3 report was introduced with new concepts for asthma management that are now centered on asthma control. The purpose of this review is to highlight features of the National Institute of Allergy and Infectious Diseases Inner-City Asthma Consortium Asthma Control Evaluation study that enhance our knowledge regarding the application of the asthma guidelines

and to provide a summary of lessons learned from that important study. We recognized that asthma symptoms and exacerbations are theoretically linked to underlying inflammation of airways but are not direct indicators of inflammation. Based on the observations from the Asthma Control Evaluation study, we were impressed that a systematic guidelines-based approach improved asthma control significantly over the course of the 1-year treatment period. (*J Allergy Clin Immunol* 2010;125:521-6.)

Key words: *Asthma, childhood asthma, inner-city asthma, exhaled nitric oxide, asthma guidelines*

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Supported in part by Public Health Services research grants HR-16048, HL64288, HL 51834, AI-25496, HL081335, and HL075416; the Colorado CTSA grant 1 UL1 RR025780 from the National Institutes of Health and National Center for Research Resources; and the Colorado Cancer, Cardiovascular, and Pulmonary Disease Program.

Received for publication November 24, 2009; revised January 13, 2010; accepted for publication January 14, 2010.

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0091-6749/\$00.00

Published by Elsevier, Inc on behalf of the American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2010.01.025

Abbreviations used

ACE: Asthma Control Evaluation
 FENO: Fraction of exhaled nitric oxide
 ICAC: Inner-City Asthma Consortium
 NAEPP: National Asthma Education and Prevention Program
 NIAID: National Institute of Allergy and Infectious Diseases
 NO: Nitric oxide

In January 2007, the *Journal of Allergy and Clinical Immunology* theme issue was devoted to the National Institutes of Health asthma networks sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute.¹ In that issue Drs William Busse and Herman Mitchell reviewed the work of the NIAID-supported Inner-City Asthma Consortium (ICAC), which is focused on issues around asthma among inner-city children.² They pointed out that for children living in inner cities, asthma tends to be more prevalent and severe.

To characterize, understand, and treat children with asthma living in inner cities more effectively, the NIAID established an Inner-City Asthma Program in 1991. The most recent program was begun in 2002 and renewed in 2009 with a goal to develop immune-based therapies for children with asthma in the inner cities, to determine the mechanisms of these therapies, to identify asthma phenotypes, and to understand the environment's effect on the development of the immune system, as well as on the immunopathogenesis of asthma in these high-risk children. Busse and Mitchell² recently summarized the contributions of 3 programs that have been part of the overall Inner-City Asthma Program. They indicated how these programs have helped us understand and treat children with asthma who live in inner cities.

Since the previous review of the NIAID inner-city asthma studies, several more studies have been completed in the ICAC, particularly the Asthma Control Evaluation (ACE) study. In addition, the revised National Asthma Education and Prevention Program (NAEPP) Expert Panel 3 report was introduced with new concepts for asthma management that are now centered on asthma control.^{3,4} The purpose of this review is to highlight features of the ACE Study that enhance our knowledge regarding the application of the asthma guidelines and to provide a summary of lessons learned from that important study.

NEW CONCEPTS INTRODUCED IN THE ASTHMA GUIDELINES

Several key terms were introduced with the new NAEPP asthma guidelines, including severity, control, responsiveness, impairment, and risk.^{3,4} *Severity* is defined as the intrinsic intensity of the disease process, and it can be measured most readily and directly in patients who are not receiving long-term controller therapy. Severity can also be inferred after implementation of optimal therapy by relating severity to the lowest level of treatment needed to maintain asthma control. *Control* is the degree to which the manifestations of asthma (symptoms, functional impairment, and risks of untoward events) are minimized and the goals of treatment are achieved. *Responsiveness* is the ease with which control is achieved by therapy.

Asthma severity and control include the domains of current impairment and future risk. *Impairment* is the assessment of the frequency and intensity of symptoms, as well as the functional limitations that the patient is experiencing now or in the past because of his or her asthma.

Risk is the estimate of the likelihood of an asthma exacerbation, progressive loss of pulmonary function over time caused by asthma, or an adverse event from medication or even death.

The assessment of severity and control provide guidance on the direction to take in stepping up or stepping down medications. In a recent theme issue on asthma in *The Lancet*, McIvor and Chapman⁵ provide an overview of the past 20 years of asthma guidelines by pointing out some of the challenges in addressing the appropriate target audience and ensuring application of these principles to improve outcomes. They point to the many ways that clinicians have not implemented key messages in these reports and support this new effort to make the guidelines practical and implementable.

Asthma is a complex disease, and it is important to assess control to understand individual patients. An assessment of control is needed to guide treatment and to help anticipate loss of asthma control and also to measure progression of disease.⁶ Asthma management in children is often complicated by parental concerns regarding adverse effects of commonly used medications.

Now that revised guidelines are available, it will be important to assess ways to integrate these principles into managed care systems. These systems can be used to examine the efficacy of treatment strategies. Despite significant advances in care that have resulted in reduction in asthma mortality over the last 10 years, certain patient populations still experience greater morbidity, and this disparity must continue to be addressed. Perhaps unique programs will have to be applied to reduce health disparities.

EFFECT OF ASTHMA ON CHILDREN IN INNER CITIES

As indicated in the review by Busse and Mitchell,² asthma has a major effect on the health of inner-city children in the United States. Since the late 1980s and early 1990s, on a national level, the prevalence, morbidity, and mortality of childhood asthma in the United States has increased, but this increase appears to have stopped; however, there is little or no indication of a decrease.⁷ Over this time period, lower-socioeconomic-status and minority children have endured the highest levels of asthma morbidity, mortality, and health care use. Although overall prevalence seems to have leveled off, this disparity has not and has even increased in some instances.⁷ In 2009, Bryant-Stephens⁸ reviewed asthma disparities in the urban environment and found African American and Latino children who live in low-socioeconomic-status urban environments experiencing higher asthma morbidity and mortality than white children. Unfortunately, interventions to reduce individual factors related to these disparities have had limited success.

The relative contribution of differences in severity or control, especially in relation to asthma exacerbations, in inner-city compared with non-inner-city populations is unknown at present. Lack of access to appropriate asthma care is a major problem in low-socioeconomic-status and minority populations and has a major effect on asthma control.⁹ The at-risk population with asthma in the inner city is more likely to be African American or Hispanic. These disparities in health care prompt the need for new information to better understand the development of asthma, risk factors associated with persistence and severity, and identification of new methods to improve management in this population.

CHALLENGES IN MANAGING ASTHMA IN INNER CITIES

There are multiple challenges facing health care professionals, as well as caregivers, in the management of children with asthma in the

urban environment. Minority urban children often receive fragmented care from multiple providers. This care is commonly episodic and exacerbation related and takes place in the urgent care or emergency department setting. The care provided frequently does not follow recommended asthma treatment guidelines. For example, in a recent analysis using Centers for Disease Control and Prevention data, Akinbami et al⁷ demonstrated that although non-Hispanic black children have higher rates of hospitalization and emergency department visits than non-Hispanic white children, their nonemergency use of ambulatory care was nearly 20% lower. Given the importance of culturally appropriate, multifaceted patient and caregiver education and support¹⁰ in the management of asthma, this lack of scheduled, nonemergency ambulatory care in the face of substantive asthma morbidity is a point of major concern.

Although some have advocated for the prescription of appropriate controller medication and focused asthma education at emergency asthma visits,^{3,4} follow-up care, especially with the primary care provider, remains central to establishing effective asthma management for this chronic illness. School-based programs for asthma diagnosis and treatment might help overcome some of these challenges; however, as noted in a recent review, these programs need to have access to quality health professional support and be practical, targeted, and cost-effective.¹¹ Furthermore, school systems sometimes create barriers to appropriate asthma care rather than being proactive in planning programs for effective asthma information and management.¹² However, even intensive school-based programs face challenges in helping patients maintain asthma control. Whatever the source of asthma care, the family must be made an equal partner in the creation and implementation of the treatment plan.

Although the Breathmobile school-based program demonstrated the ability to achieve control in 98% of low-income children,¹³ the maintenance of subsequent control varied substantively and was worsened by increased disease severity, decreased adherence, and longer time intervals between follow-up visits. This experience highlights the challenge of implementing care for an illness requiring regular adherence to daily medication, even in the absence of symptoms. The care patterns and challenges with adherence seen in urban children suggest that patients' and caregivers' beliefs about asthma might be similar to those seen in urban adults with severe asthma, in whom the "no symptoms, no asthma" belief has been shown to be associated with poor self-management, including poor adherence to controller medication.¹⁴

Facilitating the caregiver's understanding of asthma and asthma management needs to be both culturally appropriate and realistic in evaluating the barriers to care that the child and family face.¹⁰ Caregivers and patients face many stressors in their lives, the burden of which might limit their ability to maintain regular asthma medication use or attend follow-up visits. Helping caregivers and patients to understand and accept regular controller medication use, along with managing their concerns about the potential risk of therapy, is critical to optimizing adherence for both children¹⁵ and adults¹⁶ with asthma.

Fragmented care from multiple health care professionals with varying adherence to guidelines-based care does not facilitate this process.¹⁷ This can be addressed, however, by a comprehensive health care professional education program that integrates the tools necessary to deliver high-quality care. The use of an asthma counselor to help inner-city families better cope with the demands and stress of their lives has been demonstrated to be an effective approach to this daunting problem.¹⁰

NIAID Inner-City Asthma Programs

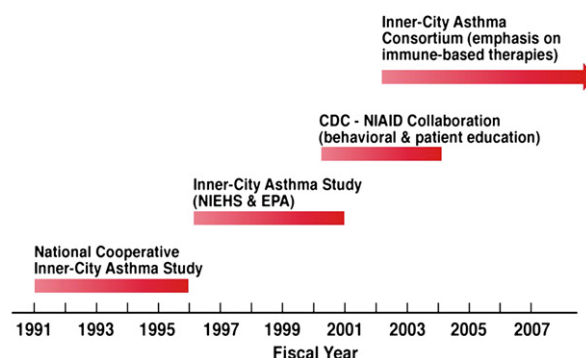


FIG 1. Timetable and summary of major collaborative studies funded by the NIAID to understand and manage asthma in children and young adults in inner cities. CDC, Centers for Disease Control and Prevention; EPA, US Environmental Protection Agency.

In another approach Cloutier et al¹⁸ demonstrated that a city-wide asthma management program delivered by primary care providers increased provider adherence to the NAEPP Asthma Guidelines for anti-inflammatory therapy from 38% to 96% and increased inhaled corticosteroid use by 25%. This pre-post analysis of the EasyBreathing program demonstrated a 27% decrease in asthma-related emergency department visits and a 35% decrease in overall hospitalization rates. This striking result suggests that an organized approach to meeting the NAEPP guidelines can have an important effect on asthma outcomes. Nonetheless, it is clear that provider education is but one key component of the comprehensive approach to urban asthma, which will be needed to identify those in need, develop appropriate guidelines-based care plans, and then implement them in a culturally appropriate manner, taking into account health beliefs, literacy, financial challenges, and family stress.¹⁹

INTERVENTIONS STUDIED IN THE INNER-CITY ASTHMA NETWORKS

In the 1980's, it became apparent that asthma prevalence was increasing dramatically and that this increase was especially rapid among minority, disadvantaged inner-city children.^{20,21} In response to this observation, the NIAID began a series of studies at centers across the United States to investigate the factors associated with asthma morbidity among these children (Fig 1). In an initial epidemiologic study of more than 1,500 children to identify factors related to asthma symptoms and exacerbations, it was somewhat surprising that no single factor accounted for the high prevalence and morbidity of asthma among inner-city children. To the contrary, many factors were found to be related to asthma symptoms. For some children, asthma morbidity was related to problems accessing care, whereas for others, morbidity was related to psychosocial problems and stress, which seemed to interfere with appropriate asthma management. Still other children were highly allergic to cockroach and other environmental allergens, which greatly increased rates of asthma hospitalization and symptoms. Higher morbidity was seen in those children who were both sensitive and exposed to environmental allergens.²² Among other children, especially among the nonatopic, nitrogen

dioxide exposure, primarily from unvented gas stoves, was significantly related to asthma symptoms.²³

In response to the clear multicausal nature of asthma morbidity in inner cities, the National Cooperative Inner-City Asthma Study (NCICAS) investigators developed a multifactorial intervention with separate modules, each of which addressed specific risk factors. This modularized approach allowed the “asthma counselors” to tailor the intervention to the specific risk factors of each child. Drawing on information gathered at baseline assessments, a risk profile was prepared for each child on the basis of his or her skin test sensitivities, environmental exposures, psychosocial factors, difficulty accessing care, lack of an asthma plan, exposure to pets or smoking, and other factors. Each exposure was evaluated in the context of the child’s allergic sensitivities, and each risk factor was scored on a scale of 1 to 10, so that counselors could tailor the intervention to address the factors that were most problematic for that child. This tailored individualized approach was found to be highly effective, with a reduction in symptom days of 13.5% among the intervention group and a 22.2% reduction in hospitalizations. The intervention was especially effective for children with severe disease, with a 39.2% reduction in symptoms among the children with more severe disease who had at least 1 hospitalization in the prior year.¹⁰

This same individualized approach used in the NCICAS study was later applied to an environmental intervention in the Inner-City Asthma Study (ICAS). In this intervention project investigators in 7 urban areas around the United States matched skin test allergy information to allergen exposure information gathered in each child’s home. This information was again combined into a risk-based approach, which linked each child’s allergic characteristics to their home allergen and irritant exposures. Accordingly, separate intervention modules were developed to address each of the major environmental allergens (cockroach, dust mite, cat, dog, mold, rat, and mouse) and tobacco smoke. A safe-sleeping zone was created for the child’s bedroom by protecting bedding with dust mite covers and by providing HEPA air filters when pets, tobacco smoke, or mold exposures were evident. In all, there were 7 possible modules that a child could receive in this tailored environmental intervention approach, and on average, the study children received 4 to 5 of the available modules. The ICAS investigators found that this tailored intervention directed at the risks for each family led to significant reductions in asthma symptoms, with 19.5% fewer symptom days among the intervention children and 13.0% fewer emergency department visits compared with the control group. The reductions in symptoms were strongly related to reductions in levels of cockroach allergen, the predominant allergic trigger among inner-city children with asthma.²⁴

These National Institutes of Health/NIAID studies among inner-city children demonstrate quite clearly the importance of an integrated approach to asthma management that includes a good asthma care plan and medical regimen along with asthma education and allergen exposure assessments, as suggested by the NAEPP guidelines. In regard to asthma guidelines, most clinical studies seek to test the effect of a single intervention on asthma management. To date, there has not been a carefully designed clinical study to determine the effect of an asthma management program using the principles of the Expert Panel 3 guidelines. Some insight on the effect of applying the principles of the asthma guidelines was obtained in the subsequently funded NIAID-supported ICAC in the ACE Study.²⁵

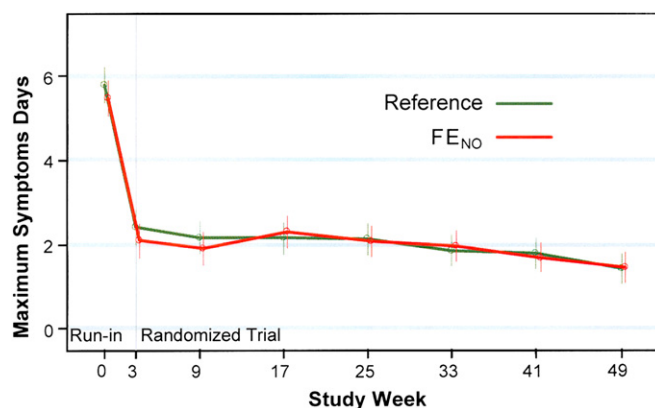


FIG 2. Maximum symptom days by study week. The first 3 weeks constitute the run-in period. Reprinted with permission from Szeffler et al.²⁵

LESSONS FROM THE NIAID’S ACE STUDY

The first major NIAID-supported ICAC study performed was the ACE Study.²⁵ We recognized that asthma symptoms and exacerbations are theoretically linked to underlying inflammation of the airways but are not direct indicators of inflammation. Our primary hypothesis was that measurement of biomarkers that are more closely associated with airway inflammation could improve asthma control by enabling treatment to be better directed toward the underlying inflammation. One such marker of airway inflammation is the fraction of exhaled nitric oxide (FENO), which has been shown to increase during periods of uncontrolled asthma and decrease during treatment with anti-inflammatory agents.

Objective

We aimed to assess the effectiveness of measurement of FENO as an adjunct to guidelines-directed management of asthma in a population of inner-city adolescents and young adults who were characterized by having high levels of atopy, allergen exposure, and poor asthma control.

Design

We conducted a randomized, double-blind, parallel-group trial at 10 centers in cities across the United States. Eligible participants were between 12 and 20 years of age and given diagnoses of asthma by physicians. We specified that those receiving long-term controller treatment must have symptoms of persistent asthma or evidence of uncontrolled disease and that all others must have both symptoms of persistent asthma and evidence of uncontrolled disease, as defined by National Heart, Lung, and Blood Institute NAEPP guidelines. At the initial visit, we assessed each patient’s asthma symptoms, pulmonary function, skin test sensitivity, adherence to prescribed drug regimen, and level of asthma control, according to 4 levels derived from the NAEPP guidelines. Medications were prescribed based on the assessment of symptom control and adherence to current treatment regimen. Control levels were assessed on the basis of the highest days and nights with symptoms over the 2-week assessment period (maximum symptom days), the lowest pulmonary function (FEV₁), the highest fraction of FENO, and adherence to the drug regimen. Level 1 denoted good control, whereas level 4 denoted poor control.

After randomization, every patient had a scheduled visit every 6 to 8 weeks for 46 weeks. At each visit, the study physician

assessed fraction of FENO, days of asthma symptoms, use of rescue drugs, pulmonary function, use of health care, adherence to treatment regimen, and missed days of school because of asthma.

For each patient, medications were adjusted at each visit according to an assessment of asthma control and medication adherence. All data for control level and fraction of FENO were entered into a computer program. The program selected a treatment option for that patient based on their randomization allocation to either a guidelines-based treatment or a guidelines plus FENO-based treatment schedule. If a patient had good control of their symptoms (level 1) and their adherence to treatment was at least 50%, their treatment would either not change or would be decreased by 1 step after 2 consecutive visits with good control. If the patient's control level was 2 and adherence was adequate, treatment was increased by a step and, if it was 3, by 2 steps. If control of symptoms was poor (level 4), physicians had the option to increase treatment by 3 steps or by 2 steps plus a course of prednisone. When adherence to treatment was 50% or greater and fraction of FENO was high relative to control levels for symptoms or lung function, patients in the nitric oxide (NO) monitoring group had an additional 1-step increase in treatment compared with what would be given to control subjects. When adherence was less than 50%, treatment was modified by using an algorithm that adjusted the indicated increase by the lack of adherence. In addition, at the same visit, the participants were re-educated on the importance of medication adherence.

Results

Maximum days with symptoms, which was our primary end point, did not differ between treatment groups over the study period ($P = .78$). Other asthma symptoms and asthma control scores did not differ between groups over the study period. Of note, there was a significant reduction in maximum symptom days that occurred after the first study visit in both groups. After the run-in period, asthma symptoms remained low in both groups throughout the study period (Fig 2).²⁵

The distribution of control level was very consistent after randomization assignment. The proportion of participants who had good control of their asthma (control level 1) stayed between 71% and 78% throughout the follow-up period. Control levels did not differ between groups: 306 (57.3%) of 534 patients had their asthma under good control (control level 1) for at least 80% of visits. In 122 (22.8%) of 534 patients, asthma control was at level 3 or 4 for at least 20% of visits (59 [22.1%] of 267 in NO monitoring group; 63 [23.6%] of 267 in control group; $\chi^2 = 0.17$; $P = .6801$). Lung function, FENO, and adherence did not differ between groups during the study. Adherence to treatment was remarkable, averaging 86.6% (SD, 27.7%) during the study.

A total of 115 (43%) of 270 control subjects (covariate adjusted value, 42.0%; 95% CI, 35.1% to 47.4%) had at least 1 course of prednisone compared with only 91 (33%) of 276 in the NO group (covariate adjusted value, 32.1%; 95% CI, 25.3% to 36.7%). However, the mean number of courses per year did not differ between groups (NO monitoring group, 0.66 [SE, 0.085] vs control group, 0.84 [0.085]; mean difference, 0.17; 95% CI, -0.08 to 0.41; $P = .14$).

Admissions to the hospital, unscheduled use of health care, or asthma exacerbations did not differ between groups but were much lower overall than they had been in the year before the study.

Observations

Whereas other studies evaluating FENO have typically replaced the usual measures of symptoms and pulmonary function with NO as the basis for determining asthma treatment, we aimed to assess its use in combination with standard symptom-based approaches to treatment. We showed that use of current guidelines for asthma treatment provided good asthma control in most inner-city adolescents and young adults and that adjusting guidelines-based treatment based on FENO levels added minimal benefit.

Asthma management that incorporated measurement of FENO in the experimental group resulted in higher doses of inhaled corticosteroids and long-acting β_2 -agonists than did standard guidelines-based treatment in the control group. This treatment option was associated with a small reduction in the need for prednisone courses but did not produce an overall improvement in asthma symptoms, lung function, or need for health care. Therefore, in the context of our study, measurements of FENO added little benefit to a carefully applied guidelines-based approach to asthma management.

CLINICAL IMPLICATIONS OF THE ACE STUDY

Based on the observations from the ACE Study, we were impressed that a systematic guidelines-based approach improved asthma control in this ACE Study population of adolescents and young adults significantly over the course of the 1-year treatment period. Adherence to treatment and study visits was excellent. Of interest, we noted that exacerbations still occurred in a large number of patients, approximately 42%, and exacerbations still followed the well-reported seasonal variation, with a peak in the fall. These findings highlight the limitations of our presently available therapeutic options when dealing with exacerbations and points to an area in which more research is needed.

Reasons for successful asthma control in this study were numerous and likely include a combination of improved communication, reinforcement of adherence, education around self-care and medication technique, easy access to high-quality care, provision of medications during the course of the study, frequent visits, and an incentive for participation. Some of these, such as a stipend, could not be applied to conventional clinical care, but other incentives could be given to encourage adherence, and certainly the clinical setting can ensure that a well-trained clinical staff responsive to the families' needs is available for all patients.

Application of guidelines-based care with high medication adherence in the ACE Study had a significant effect on impairment, specifically symptom days, and a lesser effect on risk, as indicated by the rate of exacerbations in both treatment groups. Our feeling was that exhaled NO monitoring, when added to the guidelines approach, did not reduce overall impairment measures and had minimal effect on reducing risk.

OPPORTUNITIES TO ADVANCE ASTHMA CARE

The ACE Study provided some important observations related to the benefit of a systematic approach in applying a guidelines-based approach to asthma care. After the first visit, asthma control, measures of asthma impairment remained stable, and adherence to therapy was excellent. This suggests that future studies to evaluate the application of such a system in clinical practice would be helpful. Perhaps the use of an electronic medical records-based asthma disease management program would prompt clinicians to ask essential questions regarding

symptoms, bronchodilator use, and nighttime exacerbations and more easily track their course over time. This, combined with pulmonary function measures and questions regarding adherence, could prove useful in making decisions around adjusting treatment steps. Examples of such programs include the American Academy of Allergy, Asthma & Immunology Asthma IQ program (www.aaaai.org) that is being developed and the Reach My Doctor Program that is currently being implemented as part of the Improving Performance in Practice feature of the Colorado Guidelines Collaborative.^{26,27}

Of concern was the high proportion of patients in the NIAID-supported ICAC ACE Study who had an asthma exacerbation requiring intervention with prednisone therapy: 42% in the control group and 32% in the NO monitoring group. Therefore future studies should examine methods to prevent severe exacerbations.

The future challenges for improving management of asthma in inner-city children include further studies on defining the cause of asthma; assessing the role of specific allergens, such as cockroach allergen, in predisposing to persistent asthma and asthma exacerbations; and the interaction of viral infections with the atopic phenotype. In addition, it will be important to determine whether asthma management could be enhanced by refinements in electronic medical records, community and school support programs, and public health collaboration.

We thank the NIAID for supporting the work of the Inner-City Asthma Programs, as well as their colleagues in the ICAC who designed and implemented the ACE Study and the adolescents and young adults who participated in the ACE Study.

What do we know?

- Asthma morbidity, even in the inner cities, can be reduced with a well-designed disease management program.
- Even with excellent adherence to aggressive guidelines-based therapy, exacerbations still occur and retain the seasonal patterning.
- Exhaled NO, when added to an asthma guidelines-based approach to care, does not significantly reduce asthma impairment but can have a small but significant effect at reducing asthma risk, namely asthma exacerbations.

What is still unknown?

- Do unique asthma phenotypes exist in inner-city patients with asthma compared with non-inner-city patients with asthma?
- How do environmental factors and viruses interact to heighten the risk for asthma exacerbations?
- What is the optimal treat that will eliminate exacerbations?
- Are there biomarkers or genetic features that can be used to individualize asthma care in inner-city children?
- Can immunomodulators, such as anti-IgE or allergen immunotherapy, alter the course of asthma in inner-city children who are at high risk for asthma morbidity?

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