

**Best Pharmaceuticals for Children Act (BPCA)
Sumner J. Yaffe Memorial Lecture Series in Pediatric Clinical Pharmacology
Asthma Across the Ages: Knowledge Gaps in Childhood Asthma
Presenter: Stanley J. Szefler, M.D.
12:00 p.m.–1:30 p.m. ET**

Lecturer

Stanley J. Szefler, M.D.

Moderator

George Giacoia, M.D.

Roundtable Participants

David Peden, M.D., M.S., University of North Carolina, Chapel Hill

James Fink, Ph.D., Georgia State University

Robert Lim, M.D., U.S. Food and Drug Administration

Anthony Durmowicz, M.D., U.S. Food and Drug Administration

Esteban Burchard, M.D., M.P.H., University of California, San Francisco

Introduction

Dr. Giacoia, from the Obstetric and Pediatric Pharmacology and Therapeutics Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), welcomed participants to the webinar and noted that this lecture series honors Dr. Sumner J. Yaffe, widely considered to be the father of pediatric clinical pharmacology.

These lectures are termed “bridge lectures,” because they examine the differences and similarities in treatment strategies for adults and children with the same disease. Previous lectures in this series were given by experts in their fields and addressed diverse topics. Today’s lecture, “Asthma Across the Ages: Knowledge Gaps in Childhood Asthma,” is different because it is the result of the activities of an Asthma Working Group appointed under the Initiative to Advance Pediatric Therapeutics, which is part of the NICHD/BPCA program. The Initiative reviews conditions that affect both children and adults, such as asthma, for similarities and dissimilarities in the following areas:

- Etiology
- Diagnostics
- Diagnostic biomarkers
- Pathophysiology
- Outcome measures and endpoints
- Manifestations, including phenotypic expression, pharmacometrics, natural history, response to therapy, and extrapolation issues.

The Initiative also seeks to encourage interdisciplinary collaborations of clinical, translational, and trial investigators, both in industry and in academia, who are working in complementary areas of research in pediatric therapeutics.

Today's lecture, given by the Chair of the Asthma Working Group, Dr. Stanley Szeffler, will be followed by a roundtable discussion. Because of the meeting's format, questions will only be taken in writing.

Dr. Giacoia introduced Dr. Szeffler, Director of Pediatric Asthma Research at Children's Hospital of Colorado.

Asthma Across the Ages Lecture

Dr. Szeffler explained that he would be reviewing the work of the Asthma Working Group, which spent about 2 years reviewing the categories mentioned by Dr. Giacoia. He said he knew Dr. Yaffe in medical school and had the opportunity to work in his laboratory. He mentioned that several years ago, shortly after Dr. Yaffe's death, Dr. Giacoia and Dr. Michael Reed developed a dedication to him in the *Journal of Pediatric Pharmacology and Therapeutics*, and one of the quotes from that article stated: "Sumner had a keen ability to identify promising young researchers and to guide them to appropriate funding opportunities and in many cases creating such opportunities." Dr. Szeffler said he followed Dr. Yaffe's path by including many young investigators—up-and-coming stars in the field—to participate in the Asthma Working Group. He wanted their fresh insights into the problems that need to be identified to advance asthma research.

There are several difficulties associated with asthma, one being that many medications are inhaled and do not lend themselves to pharmacokinetics (PK) comparisons with oral medications that were used in the 1970s and 80s. The inhaled medications pose certain challenges. In addition, some medications are combined medications (two medications in one), which makes it difficult to partition off the effects of each of those medications. These issues are further complicated in pediatrics by the difference in outcome measures in children and adults and by dose-inhalation issues.

The Asthma Working Group consisted of many investigators who are active in the field and some who are not closely related to asthma research, but who brought particular insights into the area. The group comprised the following investigators:

- James Chmiel, M.D., Case Western Reserve University
- Anne Fitzpatrick, M.D., Emory University
- George Giacoia, M.D., NICHD
- Thomas Green, M.D., Northwestern University
- Hengameh Heidarian-Raissy, M.D., University of New Mexico
- Daniel Jackson, M.D., University of Wisconsin Hospital and Clinics
- Heber Nielsen, M.D., Tufts University

- Wanda Phipatanakul, M.D., Harvard Medical School.

Initially, the group developed responses to high-level questions about disease progression and manifestation in children and adults. They then summarized individual responses in each area and identified and justified major issues, identified knowledge gaps, and defined short- and long-term objectives in each area.

The ultimate goal was to develop a white paper for publication. This goal was accomplished through publication in the *Journal of Allergy and Clinical Immunology's* (JACI) January 2014 theme issue, which covered "asthma across the ages." The white paper/article is in Volume 133, pages 3–13. Within this issue are several other articles prepared by members of the National Heart, Lung, and Blood Institute's (NHLBI's) AsthmaNet. One of the articles is by Dr. Rand Sutherland and Dr. William Busse about AsthmaNet priority studies, which are studies that are in progress or planned over the next several years and conducted by a network that is composed of pediatric and adult investigators. Another article, by Dr. Michael Cabana, identifies the challenges of conducting cross-age studies. One of the AsthmaNet studies is a cross-age study that has encountered problems in relation to drug delivery dosing, outcome measures, and systemic effect measures that researchers have to consider in cross-age studies. Another interesting article in this issue is about pharmacogenetics and race/ethnicity; it is representative of a study that is currently being done in AsthmaNet, and it brings forth the issues of the use of genetics in identifying response to medications.

Looking broadly at the field, a paradigm shift in the management of asthma occurs nearly every 10 years, which closely parallels advances in drug treatment and availability of medications. Asthma has moved from being viewed as relatively unpredictable, manifested by symptoms of bronchospasms, and treated as needed, to being treated by a drug that is more easily controlled; asthma research has moved to looking at areas to define control, minimize exacerbations, personalize medicine, and move the field forward toward early intervention. This progression has been complemented by advances in biomarkers, genetics, and, most of all, new immunomodulators, which are currently receiving initial attention from adult studies and hold the promise to potentially be very effective in the early course of asthma. One of the challenges being faced is how to develop a study plan that includes children down to age 1 or even younger.

Developing new approaches to personalizing asthma management raises certain questions:

- What should the early intervention strategies be, and who should they be directed to? What types of treatments and what types of outcomes?
- If biomarkers are included, which ones should be included and how should they be applied?
- If therapies are combined, how soon should that step be made and what is the appropriate combinatory therapy?
- With genetics/epigenetics, can researchers move from discovery to application?
- What is the benefit-risk of new immunomodulators at different ages, and do researchers have the right ones?

In terms of asthma drug development, the advances have mostly been directed toward allergen-induced-type pathways, or the Th2 pathways. There is a lot of excitement about using biomarkers to define the Th2 intensity, high or low, and Th2 profiles. Some of the current drugs developed are in the classifications of anti-IL-4, anti-IL-5, and anti-IL-13, which are big players in terms of asthma pathophysiology. However, there is a question of whether addressing these pathways is sufficient, given all the other pathways and mechanisms that could be related to asthma (for example, IL-17, interferon, IL-9, TSLP). If some of the pathways are hit very specifically, are other key pathways or root causes of disease missed?

The Asthma Working Group looked at the areas outlined by Dr. Giacoia and focused on four areas:

- Natural history and pathophysiology
- Diagnostics and biomarkers
- Outcome measures
- Asthma therapeutics.

The journal article details these areas and provides a summary of recommendations and key questions that need to be answered in the coming years.

Dr. Szeffler explained the rest of his lecture would focus on some of the key issues that the group addressed in the journal article and some of the questions they feel need to be answered in the near and distant future to advance the field.

Asthma Pathophysiology

The journal article's asthma pathophysiology section was headed by Dr. Chmiel.

Issue 1: There is a need for longitudinal data to determine the changes that occur in the underlying pathophysiology of asthma over the course of a lifetime and its impact upon clinical manifestations and prognosis. The reason this is important is because although asthma can present in adulthood, its origins frequently begin in childhood. One of the difficulties in studying the pathophysiology of asthma is that it clearly is different between adults and children, especially children younger than age 6. Preschool children tend to have an intermittent pattern of disease that is primarily triggered by viral respiratory tract infections.

One good study, led by Dr. Malcom Sears, is still following patients. It answers a number of questions that pediatricians and parents ask about children with asthma and well describes different patterns of the disease in terms of onset, remission at times, relapse, and intermittent courses. It identifies associated features of the disease, such as dust mite sensitivity, allergen sensitivity, and time of onset of disease, that are linked to the different phenotypes. A remarkable finding from this study is that there are differences in lung patterns that emerge in terms of measures of airway obstruction. This study began with children who were age 9 and is now following them into adulthood (so far up to age 40). A couple of key factors are that those with persistent disease tend to have lower pulmonary function, which is manifested by the time they

reach adolescence. Thus, something is occurring in early childhood, or perhaps they were born that way. The gender-specific patterns are also different; for persistent wheezing, both females and males start at a lower maximal height, but there is a difference in males versus females in terms of those who have relapse in disease. With relapse, the males have persistent lower maximal height.

Issue 2: There is a need to better understand the relationship between the severity of asthma and the inflammatory response. The magnitude of airflow limitation and air trapping in children ages 6 to 12 is significantly less than in adults, and it seems to correlate with structural changes. The airflow obstruction typically is episodic in nature and reverses either spontaneously or with medications.

Issue 3: There is a need for improved measures for determining lung function in children younger than age 6. Although most adults with asthma typically have a progressive loss of lung function over time, lung function is maintained in a relatively normal range in the vast majority of children, outside of exacerbations. Children ages 5 and older can reliably perform spirometry, but lung function measures in preschool-aged children are difficult to obtain.

Issue 4: There is a major need for an improved method of assessing inflammation noninvasively across the age groups. Most of the data regarding the underlying airway inflammatory response in asthma are derived from studies conducted in older children and adults. It is difficult to get these measures in children younger than age 8.

Manifestation and Natural History of Asthma in Childhood

The manifestation and natural history section was headed by Dr. Jackson.

Issue 1: There is a need to develop new strategies for the prevention of asthma. Asthma inception often occurs during the preschool years, and the events that occur during this time have lifelong consequences. Current strategies have been ineffective in preventing asthma. However, as understanding of the factors involved in asthma inception grows, novel strategies of asthma prevention (such as new immunomodulators) should be pursued.

Issue 2: There is a need to develop new strategies for the prevention of viral-wheezing and asthma exacerbations. Asthma exacerbations are more common in children than adults, and current therapies are only partially effective in preventing them. Thus, even the best treatment circumstances are still ineffective at preventing asthma exacerbations.

Issue 3: There is a need to develop greater understanding of gender differences in relation to the inception, persistence, and remittance of asthma, and how gender relates to response to therapy. Gender is an important factor in the natural history of asthma, as boys outnumber girls during the first decade of life, while women outnumber men (and tend to have more severe disease) in adulthood. This “switch” appears to occur during puberty, but the underlying factors are poorly understood.

Issue 4: There is a need to identify which children will develop progressive loss of lung function over time and whether this might be linked to a pattern of chronic obstructive lung disease that may be mixed with an early asthma pattern. Lung function is relatively well maintained in the majority of children, however, progressive loss of lung function occurs in a subset of individuals. This has significant consequences in terms of subsequent morbidity associated with asthma as children progress through the teenage years into adulthood.

For this topic, the journal article addresses the following:

- Inception of asthma
- Progression of asthma
- Importance of asthma exacerbations
- Unanswered questions.

Unanswered questions listed in the article include the following:

- What inflammatory phenotypes are present in children, what is their long-term stability, and how do they relate to airway remodeling?
- What factors are responsible for triggering asthma onset?
- What factors are associated with progressive disease?
- What is the influence of sex on asthma in relation to inception, prevalence, persistence, remittance, and response to therapy?
- How do asthma exacerbations contribute to long-term outcomes?

Diagnostics

Dr. Phipatanakul led the diagnostics section of the article.

Issue 1: There is a lack of objective diagnostic tools in young children, particularly for how they relate to disease management and natural history of disease. There is a paucity of data in young children to determine transient, viral-induced wheezing versus more chronic, persistent wheezing that becomes established asthma. There is also a need for better diagnostic and objective tools for asthma and asthma management to monitor disease activity. It is difficult for young children to implement and properly do spirometry and lung function examinations. In addition, longitudinal follow-up is needed to determine the natural history of asthma and what predicts ongoing severe, persistent asthma.

Issue 2: There are no true “biomarkers” that fit all the criteria in the field of asthma. Instead, asthma is considered a clinical “syndrome,” and diagnosis and management are therefore largely based on symptoms. A true biomarker is needed that meets the following criteria:

- Distinguishes “normal” from asthma
- Changes with exacerbations and normalizes with treatment
- Is stable over time and consistent across the age spectrum.

More large studies are needed in children to investigate whether a biomarker can predict response to therapy or predict natural history of disease.

Genetics of Asthma and Asthma Pharmacogenetics

The genetics and pharmacogenetics section was led by Dr. Fitzpatrick.

Issue: There are limited studies of asthma genetics and asthma pharmacogenetics. The majority of the genetic research has focused on general populations of European white descent, and most of the individuals in these studies were adults. There is considerable variability in the clinical response to asthma medications in both adult and pediatric populations. Thus, there is a need for hypothesis-driven pharmacogenetic studies with stratification for genes that are known to regulate PK in order to tease out gene-function relationships that are relevant to asthma pharmacology.

The article describes available information and current studies, including:

- Exhaled nitric oxide
- Exhaled carbon monoxide and pulse carbon monoxide
- Exhaled breath condensates
- Airway inflammatory cells
- Urinary biomarkers
- Serum biomarkers
- The role of computed tomography and magnetic resonance imaging.

All of these topics are in the discovery stage, and a series of articles published in the March 2011 issue of *JACI* reflected the work of a National Institutes of Health Task Force about outcome measures. Those articles have become a template in terms of selecting outcome measures for asthma-related research.

Unanswered questions that are raised in the article include the following:

- Are there acceptable alternative approaches to lung function testing in young children?
- What biomarkers can be used to predict asthma progression in young children?
- What are the performance characteristics of available biomarkers, including ease of collection and stability and long-term validity across the age groups?

Asthma Outcome Measures

Dr. Fitzpatrick also led the outcome measures section.

The outcome measures in clinical trials are not necessarily the same for adults and children, and there have been no attempts to standardize asthma outcomes across the spectrum of pediatric asthma trials. Pediatric-specific outcome measures are needed for clinical trials to better assess pharmacologic efficacy, particularly for children younger than age 5. There are important differences between adults and children that merit attention.

Topics addressed in the outcome measures section include:

- Biomarkers
- Spirometry
- Composite questionnaires
- Asthma exacerbations and health care use
- Other general considerations for outcome assessment.

Unanswered questions for this area include:

- Should outcome measures for pediatric studies be the same as for adults?
- Should composite measures be preferred in children over single outcomes, such as lung function or exacerbations?

Clinical Pharmacology

The clinical pharmacology section was led by Dr. Green.

The article identifies areas in need of further definition and age-related studies, including:

- Inhaled corticosteroids
- Intravenous β -adrenergic agonists
- Omalizumab
- Anticholinergics.

There are significant gaps in the use of these medications, including asthma-inhaled corticosteroids. Issues for these drugs include the following:

- They are commonly used in children <5 years old, which is outside the age range of scientific evidence and U.S. Food and Drug Administration (FDA) approval.
- They are usually delivered in these children by metered dose inhaler (MDI) devices with spacers, but there are no data on drug delivery to the lung.
- Safety in these growing children is unknown in terms of systemic absorption and incidence of adverse effects.
- There is limited evidence of efficacy in these children.

There are specific needs for studies in children <5 years old related to:

- PK comparing nebulizer with MDI/spacer delivery for dose-response and systemic absorption information
- Efficacy in relation to safety analysis of inhaled corticosteroids in this age group
- Improved outcome measures relevant to this age group.

For intravenous (IV) beta agonists, there is a need for information about:

- IV beta agonists commonly used in pediatric ICUs for severe refractory asthma
- Important gaps in clinical pharmacology of beta agonists in the pediatric population
- Uncertainty in efficacy
- Variability in clinical application (in relation to dose and indications)

- Unknown dose-related risks of cardiovascular side effects
- Lack of appropriate pediatric formulations.

There is also a need for:

- Conducting appropriate studies in relation to age-appropriate formulations and asthma assessment tool(s) that are appropriate for age, disease severity, and severe unstable asthma cared for in ICU
- Tying together the physiologic parameters
- More information about age-related PK and pharmacodynamics (PD)
- More information about age-related efficacy and safety.

For anti-IgE, issues include:

- There is no therapy for disease modification or prevention in children.
- Omalizumab (anti-IgE antibody) is only approved for children >12 years age.
- Experimental data suggest use of omalizumab early in childhood may prevent or modify the course of asthma, but there is still concern about the potential for serious adverse effects, including delayed anaphylaxis and malignancies.

Desirable anti-IgE studies include controlled clinical trials in children <5 years, including safety data, immunologic effects, and efficacy data. There is also a need for successful studies for:

- A validated asthma predictive index
- Physiologic pulmonary function testing
- Age-appropriate immunologic testing.

The anticholinergics have gained attention and are commonly used in acute asthma in children, despite the absence of FDA approval. They are considered effective in chronic obstructive pulmonary disease, which is “an adult disease,” therefore the FDA approval does not extend down to children. A limited number of recent clinical trials show that long-acting anticholinergics are effective in adults. They are currently being evaluated in terms of getting labeling, and children down to around age 12 are included in the trials.

Asthma Therapeutics

Drs. Nielsen and Green led this section of the article.

Dr. Green looked at areas of need, not only in terms of the drugs, but in terms of the therapeutic indications. In particular, there is a need for:

- Continued long-term suppression of asthma exacerbations, particularly as it contributes to airway remodeling
- More information about acute therapy to reduce the intensity and duration of severe exacerbations, particularly those that require intensive care
- Approaching disease prevention and change in progression and moving more toward total amelioration of the disease.

The unanswered needs and questions around therapeutics include:

- Identifying the age-appropriate inhaled drug administration technique that provides optimal lung delivery of medications
- Determining which treatment strategies are effective in preventing and modifying the course of asthma
- Identifying the studies that should be conducted to appropriately label medications for the management of acute asthma exacerbations in children
- Developing age-appropriate formulations for therapeutic agents, especially those used in the hospital setting.

Article Summary

Some of the article's general conclusions include the following:

- Many asthma medications are inadequately labeled in children; in general, the younger the child, the less specific the label.
- There are several new medications on the horizon, including a number in the biologic modifier category.
- It would be useful to develop a registry of ongoing cohorts to form the basis of collaboration to understand the early origins of asthma. An upcoming *JACI* article will summarize the experience among cohorts and lessons learned. The most imminent need is for cohorts to work together to look at the data and identify areas of comparison and contrasts to develop future studies, not only to take the lessons learned and develop what is known, but to develop better studies for the future and address key questions.
- It is important to identify clusters of biomarkers that may be associated with or reflect disease activity. This is important for diagnosis and treatment.
- It is important to focus attention on validating outcome markers for symptoms assessment, especially in young children.
- Efforts should be made to develop clinical trials for early intervention, including dose ranging and PK/pharmacodynamic studies for primary prevention.
- Defining therapeutic strategies to alter progression of disease is also a high priority, particularly identifying risk factors for the subpopulation that is susceptible to disease progression.
- Age-specific drug formulations should be developed.
- Continued efforts should be directed to defining effective strategies to reduce the risk of exacerbations.

If these strategies are addressed, a reduction in asthma mortality and morbidity associated with urgent care needs and altered quality of life should continue.

Dr. Szeffler noted that the members of the Asthma Working Group wanted to thank the NICHD for the opportunity to summarize this important information that will serve to stimulate future studies of asthma in children. They also wanted to thank *JACI* for allowing publication of this report.

Dr. Szeffler noted that many members of the NICHD Asthma Working Group are also members of the NHLBI AsthmaNet and the National Institute of Allergy and Infectious Diseases (NIAID) Intercity Asthma Consortium. The working group has communicated its work to these research teams so they can address gaps in information. This working group had an immediate impact by raising the issues identified to collaborators and had a significant impact on the study designs of current and proposed studies. Dr. Szeffler thanked the NICHD, which has a great interest in drug development for children, and said he hopes the Asthma Working Group has helped move the field forward.

Roundtable Discussion

Dr. Giacoia introduced the roundtable participants and explained that each will give a response to the lecture and answer audience questions.

Dr. Peden

Dr. Peden said many aspects of Dr. Szeffler's presentation are important, in particular, the lack of biomarkers and the lack of a really well-defined definition of exacerbation. These deficiencies make it difficult to have a standard, unified approach to conducting clinical trials that can identify new treatment paradigms, new uses of existing agents, and testing for new agents. He noted he was co-chair of a workshop sponsored by NHLBI and NIAID, and his subcommittee focused on exacerbations. After an extensive literature review, the subcommittee found that the only fairly solid measure of exacerbations was a decision by a provider to use systemic corticosteroids, or enhance the use, so there is a big gap in biomarkers. He said that in pediatrics, a lot of the biomarkers will need to be serum, urine, or radiographic markers that are relatively noninvasive and will need to be used down to young ages, particularly for prevention or mitigation of ongoing disease. Another area in addition to immunomodulators that could be influenced is routine allergen immunotherapy or mitigation of allergy in those children who have allergy as a major risk factor. Another important area is approaches that could decrease severity of rhinovirus and other upper respiratory tract viral infections early in the course of a cold in those who are susceptible so that medication can be given early on.

Dr. Giacoia replied that the NICHD has been interested in biomarkers for many years. It has renewed initiatives for studies being done to extrapolate biomarkers for pediatrics from those that have been demonstrated as effective in adults. He said he will send information along and encourages participation in these studies.

Dr. Fink

Dr. Fink stated that his interest is to understand aerosol delivery systems in small children. To date, virtually no manufacturers of inhaled medications for asthma have an approved label across the range of pediatric sizes and ages. For many years approval only went down to age 6, then a few went down to ages 2 or 3, but infants and toddlers are still unrepresented in terms of the basic research to have these drugs approved. Most drugs approved for inhalation were studied in

older children and in adults using aerosol generators combined with a mouthpiece. Although some studies show similar dose per kilogram relationships across pediatric patients down to about age 4 with MDI nebulizers, very few of the patients studied were age 4 or younger. It is reasonable to assume that pulmonary deposition, clinical response, and PK/PD changes occur with size and age, but this has not been well studied or well defined. Consequently, there are not sufficient data to guide changing inhaled doses, which were defined for larger children or adults, for application to infants and small children. Pediatricians prescribing for infants and small children face the dilemma of prescribing drugs that are not approved for these age categories with little or no guidance as to how to adjust the administration method, dose, and frequency of medication.

Additional research is required to better understand how those dose requirements and responses vary with age and size, down to the smallest patients. This is complicated by the difficulty of reliably administering aerosol to infants and small children. Although there have been great changes in technology and improved deposition, there are huge variances between different techniques that are used. There are also problems in empirically monitoring infant and toddler responses in both ambulatory and ICU settings.

Several trials of enhanced steroids in this population have failed, in part because of the weakness of observational diaries used by caregivers or parents to monitor response. Because of the difficulties and costs associated with clinical trials in these populations, stronger incentives need to be established with industry and better support given for funded research. As recommended by the European Medicines Agency (EMA), researchers need to study safety in clinical trials for the full range of pediatric patients who might benefit from the specific medication when using size and age-appropriate interfaces.

Dr. Fink noted it is interesting that no MDI can be used with a neonatal infant, or even toddlers up to around age 3, without the benefit of a valve-holding chamber. Yet no drug has been approved based on efficacy and safety studies with that kind of interface; all have been studied with just the mouthpiece. There is a huge difference between the various valve-holding chambers and spacers, which could constitute an order of magnitude difference in inhaled dose.

In vitro models have come a long way in the past 5 to 10 years and may provide clues to help estimate drug delivery in smaller pediatric patients. However, there is not a lot of continuity across industries or academics in terms of sharing these models so that meaningful *in vivo/in vitro* correlations can be established. Even the *in vivo* models are only a guide as to where to start the studies.

Clinicians and prescribers need to understand the device options that are available and understand which patient interface works best at each stage of growth and development, with the cooperation of the individual child. A system that works well for a 6-month-old child may not be as effective for a 2-year-old. There are things that can be done in the short term, but in general, there is still a lot to learn about aerosol delivery in this population.

Reply: Dr. Szeffler said these comments are very important and that although the biomarker question is one that the Working Group paid particular attention to in the article's summary, it is a rapidly developing area. Studies have been done within the NIH asthma networks, particularly the Childhood Asthma Research Education Network, where biomarkers such as exhaled nitric oxide were identified and associated with positive response to inhaled steroids, and urinary leukotrienes were associated with positive response to leukotriene antagonists. For some biomarkers, even though the studies exist, additional validation is required and clinical application needs to catch up.

Dr. Szeffler also noted that Dr. Peden's point about allergen immunotherapy is good because that is one of the drugs that in some studies has been associated with alteration of the course of the disease. It has been found that researchers have to be selective in terms of the allergen identified. In addition, better indicators are needed to determine the most relevant allergens and whether they can be limited and focused in order to alter the course of the disease. The Intercity network is particularly interested in cockroach and mouse allergens.

Dr. Szeffler said Dr. Fink's comments about drug delivery are right on target. It is an area that "the younger the age group, the less that is known." Thus, there are wide gaps in terms of the degree these medications are used and of the proportion of information available so the drugs will be used judiciously. Many of the doses are extrapolated from adult doses, and many of the formulations are the same as those used in adults. Effects on growth have been identified with inhaled steroids that may be related to age and the milligram per kilo dose, which is a result of the formulation and not necessarily the intention.

Dr. Giacoia seconded Dr. Fink's plea for research on inhalers. He noted there is an initiative for pediatric formulations that includes drug delivery systems, and he would like researchers to move forward in this field.

Dr. Burchard

Dr. Burchard stated that his main interest is racial differences in drug response, a difference also seen across sex. The differences have been demonstrated by studies such as the Salmeterol Multicenter Asthma Research Trial (SMART), which demonstrated racial differences in response to long-acting beta agonists and led to a black-box label warning. Published research has also shown inherent serum resistance among African Americans; this is also true for inhaled steroids. It has been demonstrated that African Americans do not derive the same augmentation of bronchodilator response as non-African Americans.

AsthmaNet has initiated longitudinal pharmacogenetic studies, with one launching this month, but they are relatively small studies. In the past, the vast majority of studies focused on European populations. As of 2011, 96 percent of most contemporary pharmacogenetic studies were performed on people of European descent. The field of genetics and pharmacogenetics in non-European populations is novel and uncharted territory. When one looks at biomarkers, there are well-known racial and ethnic differences with respect to nitric oxide, even by age. Even a

biomarker of anti-IL-13 efficacy is well known to have different diagnostic efficacy in older individuals versus children.

Many of the current pharmacogenetic studies are being stratified based upon a single gene and a single mutation in that gene. But it is well known that genetic ancestry modifies some of the genetic variances that are associated with pharmacological response. There are insufficient studies in minorities, which is a travesty. There has only been one pharmacogenetic study of inhaled corticosteroids, and it was largely restricted to children of European descent in a camp study. There is a dearth of studies in minority populations, and these studies need to be very comprehensive. They need to include diverse populations across the age range and be between boys and girls/men and women. They also need to look at other factors associated with pharmacologic response, in addition to environmental factors such as tobacco smoke exposure and air pollution, which are well documented to attenuate bronchodilator response; these factors account for the social differences in populations and access to care. What has been done thus far is interesting, but it falls short of the goal of making health care available to all populations, as well as making scientific advances accessible to all populations.

Response: Dr. Szeffler said all of Dr. Burchard's comments are very relevant and this area is particularly highlighted when looking at the Centers for Disease Control and Prevention statistics for asthma. This area needs better approaches, be it through access to care or better understanding of treatments. This issue is somewhat identified in the Asthma Working Group's article, although it is identified more specifically in the associated article in the same issue by Dr. Victor Ortega and Dr. Deborah Meyers. A significant amount of time, effort, and funds have been invested into the AsthmaNet study Dr. Burchard mentioned, so hopefully it will be successful in terms of recruitment and some of the genetic areas that will be explored. Another challenge is that even though there are distinct populations, there is admixture, so there are a lot of variables that need to be teased out in relation to response and personalizing treatments.

Dr. Peden agreed and said that particularly with pharmacogenetics, because most studies have been done on European populations, there is not information about those who are at particular risk—from a public health perspective—in the United States. Ethnic-specific genetic risks and ethnic-specific pharmacogenetic aspects have not been captured in previous studies, so determining what kinds of studies are needed or how existing studies can be leveraged to glean that information is critical.

Dr. Lim

Dr. Lim said that in regard to efficacy and extrapolation, he divides the pediatric population into three groups: children/adolescents ages 12 to 18, children ages 5 to 11 (old enough to do pulmonary function testing), and children younger than age 4 (who cannot do pulmonary function testing). Children/adolescents ages 12 and older are generally included in adult asthma trials; however, evidence for efficacy is generally derived from the replicated trials performed in the adult asthma program. For children ages 5 to 11, evidence for efficacy is derived from a body of data that can consist of replicated trials in this age group taken together with replicated trials

for evidence of efficacy in trials for children ages 12 and older. Generally, the primary endpoints used are forced expiratory volume in 1 second (FEV1) related, and although it is recognized that this may not be the only endpoint that should be considered, improvement in FEV1 would be evidence for efficacy. For children younger than age 5, extrapolation cannot be used for locally acting drugs (such as inhaled steroids) because systemic exposure does not really reflect efficacy. Thus, demonstrating similar PK in exposures between different populations would not really imply similar efficacy. To demonstrate efficacy in the lower age group, an efficacy trial with clinically relevant endpoints would be needed, which leads to a second issue of the relative paucity of endpoints for this age group. There is a need for more, or other, endpoints that can be assessed for efficacy in the patient age group that cannot perform pulmonary function testing.

The third issue is delivery method. A lot of these drugs are delivered by an MDI, and all children age 5 and older require use of a spacer; however, the issue comes up that spacers are approved in a parallel regulatory process. The MDIs are usually approved as general use devices and not approved to be used with a specific drug. Spacers can affect local drug delivery, which can then affect local drug deposition and lead to differences in drug efficacy for the same MDI. Because of this issue, the FDA has generally not approved MDIs for age groups that would require a spacer. In clinical care, use of a spacer in children (particularly in children younger than age 5) is standard of care, so it would be helpful to provide labeling that is more informative to health care providers. In response to the BPCA and pediatric labeling legislation, the FDA has gotten some spacer data and incorporated it into labels; those labels have included *in vitro* data, which estimates dose delivery, and some PK data that compares exposure with and without a spacer.

Response: Dr. Szeffler said these are valid points, and in the design of AsthmaNet and Intercity trials, they had to consider these points and others. Questions have been raised during cross-age studies, such as “Are there unique features that can lead researchers to better accuracy rather than age and years?” and “Are there other features, such as Tanner staging or biomarkers, that may be more refined in regards to drug-related information?” Although the age categories are helpful in terms of defining studies and setting parameters, they are fairly rigid in terms of specifications based on age. He noted that the spacer devices discussed by Dr. Lim are a problem because of practical issues; it will be hard to study a drug with one spacer and then have that spacer taken off the market a couple of years later or replaced by another spacer. Researchers need to brainstorm about how to give clinicians adequate information about the combination of the drug and the spacer.

Dr. Fink responded that the EMA has an approach that if a drug is to be approved for children with a specific MDI, the spacer needs to be called out and become part of the label claim (as is done in the United States with nebulizers). This way the burden is on the drug manufacturer to have a relationship with the spacer manufacturer so they can assure the device does not fall out of access during the lifecycle of the drug. Maybe some guidance or regulation in that direction would help.

Dr. Peden said the pragmatic issue is that although researchers can try to get data that suggest an indication, the practical implementation of those recommendations often becomes an issue. For

example, “Do people really use the spacer devices the right way?” Studies need to be designed for the younger age groups for device use during exacerbations when the ability to use a spacer correctly is compromised. There are a lot of practical issues that influence how well recommendations go through to families. He said he appreciates the regulatory requirement to have firm data on which a precise indication can be given, although it can be frustrating to pediatric providers to be left in a gray zone where they often have recommendations and expert panels, but not much official guidance from the FDA. It would be helpful to provide regulatory “best current practice” data to the pediatric community.

Dr. Durmowicz

Dr. Durmowicz said everyone’s points are well taken and that there is somewhat of a regulatory disconnect in young children between drug delivery and how drugs and devices in the United States are approved. This is a regulatory constraint that the FDA has been trying to work around. The BPCA and Pediatric Research Equity Act have helped the FDA by putting specific spacer data in some of the pediatric MDI products. He said locally inhaled products are tending to go more to the dry powder inhaler mode, which is even less able to be delivered to a younger child who cannot generate the type of flow needed to overcome the resistance to deliver the medications. The FDA is trying hard and will continue this work.

Panelist Discussion

Dr. Giacoia asked the panelists to react to cross-age studies in asthma, to give their opinions, discuss limitations, and state where adolescence fits into the picture in relation to similarities and differences between adults and children.

Dr. Szeffler stated that Dr. Cabana’s article in the *JACI* theme issue addresses some of the problems that were addressed and encountered in setting up the study about best treatment response in African-American populations. That particular study brought about great debate as to whether to design the study across race or across age, as there were implications in relation to study design and cost. It was decided to focus on both race and age, and challenges were encountered in terms of drug dosing, delivery device, systemic absorption, outcome measures, and so on; adolescents were a particular challenge related to where they fit into the dosing scheme and pulmonary function parameters, for example. A lot of forward thinking needs to be done, and he said he is grateful that the government has recognized these issues and has provided forums for discussing and conducting the studies.

Dr. Peden agreed, saying there are a lot of efforts to try to address the unique issues for pediatric approvals for interventions in children age 0 to 4. It would be useful to provide clear guidance as to what endpoints and yardsticks will be able to support these studies and lead to product approval. Obviously, lung function is not feasible in children age 0 to 4, so there will need to be specific guidelines about whether endpoints will be onset of asthma or frequency of wheezing events or exacerbations, and whether or not a specific intervention over a period of time lessens the frequency and duration, and perhaps severity, of exacerbations. There is evidence that

frequency and severity of exacerbations have an impact on lifelong risks for disease. Researchers may want to look at interventions with these endpoints in mind and ask whether it is likely that by intervening with these particular events there will be a lifelong effect that may not be manifested for years after the intervention.

Dr. Fink agreed that it is hard to keep the yardstick going when moving into a whole new set of criteria that are used to judge response to medication. It is hard for governing agencies to come up with guidance in areas where so little has been effectively adopted in the pharmaceutical community; collaboration with pharmacy, government, and research is necessary for this area so that a rational standard can be developed to help guide the research and drug approvals.

Dr. Burchard said this issue has been a conundrum for the FDA. In the last 2 years, a meeting was convened to address admixture, which has potential for variation in genetic ancestry, and its implications for pharmacologic studies. Many studies are conducted outside of the United States and the results are extrapolated back to the U.S. population. For example, Brazil and India have very heterogeneous populations, and many studies are done in those countries. It is not clear whether drugs that are efficacious in one country are generalizable to the U.S. population, and the FDA is grappling with how to address this issue. It is an issue that trickles down to the pharmacologic and pharmacogenetic studies that AsthmaNet is conducting. It is necessary to be very mindful of this potential confounder in all of the clinical research that is going on.

Dr. Giacoia pointed out that cross-age studies are applicable to many condition and are an area of much discussion.

Audience Questions

Dr. Giacoia presented an audience question and asked panelists to respond: “In relation to progress with biomarkers for children, whose job is it to develop them? The pharmaceutical industry? Academia?” Dr. Szeffler responded that this in an important area where the reverse of what is currently happening should occur; there has been a push to separate academia from industry based on aspects of conflict of interest, and breaking this communication is the worst direction in which the field can go. Industry develops the drugs and often develops easier-to-use biomarker applications, so there needs to be dialogue to indentify these things. The tipping point was reached with exhaled nitric oxide and recent publications about serum periostin. Continued dialogue is important to determine what can be applied prospectively to validate observations and perhaps use available databases retrospectively. Many times studies are completed and the data are filed, and if studies are designed to collect the right samples, researchers can go back and look at relationships between biomarkers and response. The one precaution is that the biomarkers may be different in terms of their levels in children, as compared with adults.

Dr. Giacoia emphasized that the NICHD is very eager to stimulate dialogue and interaction between regulators, pharmaceutical companies, and investigators. The next American Society for Clinical Pharmacology and Therapeutics (ASCPT) meeting in March includes all the stakeholders, who will try to move the field forward.

Dr. Peden commented that in regard to biomarker development in children, one thing to consider—beyond dialogue and the economics of doing studies—is what kinds of samples could be collected from children at a particular age, whether it be urine, blood, or nasal secretions, and then how to apply metallomics, proteomics, and other unbiased or unsupervised approaches to validate them for meaning to demonstrate that intervention is effective. Investigators need to mimic what is happening in the genetics and genomics field, as there may be signals that academics have not thought to look for. There may already be children with well-defined exacerbations, and by getting as many samples as possible from those databases, some hypothesis generating could occur. He noted the importance of getting samples that are actually achievable if they are going to be used on a population basis for drug approval.

A participant from University of California at San Francisco commented that he was part of the study led by National Jewish Health in which the researchers looked at nasal gene expression and strongly correlated that to lung biopsy gene expression in children. There was as much as an 87 percent correlation between gene expression patterns, and those patterns were able to differentiate the Th2-high and Th2-low children with asthma (which was previously demonstrated by a study published in the *New England Journal of Medicine*), which is a sub-phenotype of asthma that more responsive to anti-IL-13 therapies. It is difficult to do clinically useful biopsy samples in children, particularly bronchial biopsies, so nasal samples might be a good proxy for going forward and testing gene expression patterns and looking for biomarkers in those tissues.

Industry submitted a comment stating that they are challenged by the identification of age-specific biomarkers that may change with age. They asked “How does the FDA take this into account when using outcome measures in clinical trials?” In reply, a participant stated the FDA has a new biomarker qualification group within the Center for Drug Evaluation and Research that looks at biomarkers and how drug companies and others develop them. Some biomarkers might only be relevant to a certain part of the asthma spectrum or asthma age population. The way this issue is handled is relatively new, and the FDA is working to develop an internal policy. But if a biomarker is only relevant for part of an asthma population, it brings up the question of whether it can be used in the entire population in regard to some type of extrapolation; this issue has not been talked about much internally.

Dr. Giacoia shared another audience comment: “If specific biomarkers of disease are needed, but lacking in children, given that evidence is weak or lacking in this area for adults, should this be taken into consideration when prioritizing areas of unmet needs?” Dr. Szeffler responded that if the question is whether issues the article points out for children are also relevant for adults, he completely agrees. The area of progression of disease around asthma and biomarkers is limited, if not scarce. Other disease fields, such as cystic fibrosis, have actively identified biomarkers associated with rapid loss in pulmonary function, which is very important in terms of monitoring disease activity and drug efficacy.

Dr. Giacoia emphasized that this discussion will be continued over time. There were many participant questions that could not be answered today, but they will be posted on the BPCA website so Dr. Szefler and the panelists will have the opportunity to respond to them. He said the NICHD is trying to stimulate ways to move forward in a systematic fashion, and he invited all participants to attend the ASCPT meeting and join in the group discussion. Dr. Giacoia thanked Dr. Szefler, his working group, and the panel members for their efforts and closed the webinar.