

Asthma across the lifespan: Time for a paradigm shift



Stanley J. Szeffler, MD *Aurora, Colo*

We have a unique opportunity to significantly reduce the worldwide burden of asthma in children and affect respiratory outcomes in adults. However, this will require a paradigm shift that is directed at altering the natural history of asthma, reducing asthma exacerbations, and preventing long-term adverse outcomes of childhood asthma. Attention should continue to be directed toward minimizing risk, as well as impairment, with a goal to achieve optimal control. Based on several National Institutes of Health studies conducted over the last 10 years, we now have the tools necessary to accomplish this goal. The tools include assessment of lung function over time or defining trajectories of lung growth, the Composite Asthma Severity Index score, a panel of useful biomarkers, the Seasonal Asthma Exacerbation Prediction Index score, and rapidly advancing technology that includes adherence monitoring. Future guideline revisions should consider incorporating recommendations to follow spirometry over time and defining trajectories of lung growth to assess risk for reduced lung growth and early decline, asthma burden by using biomarkers to select and monitor therapy, assessment of social determinants of health, evaluation of risk for seasonal exacerbations, and consideration of electronic adherence monitoring for difficult-to-manage asthma. Guidelines should continue to include a core dedicated to the diagnosis and treatment of intermittent and mild and moderate persistent asthma and include additional sections dedicated to the management of severe asthma. (J Allergy Clin Immunol 2018;142:773-80.)

Key words: *Asthma exacerbation, asthma guidelines, Composite Asthma Severity Index, Seasonal Asthma Exacerbation Prediction Index, trajectories of lung growth*

We have a unique opportunity to significantly reduce the worldwide burden of asthma in children and affect consequent respiratory outcomes in adults. However, this will require a

paradigm shift directed at altering the natural history of asthma, reducing asthma exacerbations, and preventing long-term adverse outcomes of childhood asthma. To do this, we should now take steps to incorporate key lessons from several major National Institutes of Health (NIH)-supported studies that were designed to fill gaps in the National Asthma Education and Prevention Program (NAEPP) asthma guidelines published in 2007.¹ These NIH studies conducted over the last 10 years have provided us with the tools necessary to reduce the worldwide burden of asthma in children and affect respiratory outcomes in adults. Successful use of these tools will require a paradigm shift that focuses attention on the risk domain in asthma control.

The essential tools proposed to enable the approach to asthma to be more proactive and less reactive include (1) assessment of lung function over time (defining trajectories of lung growth), (2) the Composite Asthma Severity Index (CASI), (3) a panel of useful biomarkers, (4) the Seasonal Asthma Exacerbation Prediction Index (SAEPI), and (5) use of adherence-monitoring technology. The goal is to improve not only short-term symptoms but also the long-term consequences of the physiologic and biologic processes leading to persistent asthma, severe asthma, and chronic obstructive pulmonary disease (COPD). This rostrum is thus directed to members of expert panels to embrace these concepts in their revisions to asthma guidelines or proposed strategies and also to clinicians to consider adapting these tools in their clinical practice to affect immediate care of patients with asthma, especially children.

CURRENT ASTHMA MANAGEMENT

Asthma guidelines were introduced in the United States in 1991 to standardize and organize asthma care and address an increasing trend in asthma mortality. This goal has been accomplished by an actual reduction in asthma mortality; however, asthma hospitalizations and urgent care visits have been reduced minimally, and there are significant disparities in morbidity across populations caused by social determinants of health, including housing and income.²

For the past 50 years, we have seen paradigm shifts in asthma management about every 10 years (Fig 1). With the last update of the NAEPP Expert Panel Report 3 (EPR-3) guidelines in 2007,¹ this paradigm shift focused on achieving asthma control defined within 2 domains: impairment and risk. *Impairment* consists of daytime and nighttime symptoms, rescue medication use, and pulmonary function and scores on questionnaires to assess these measures over a short-term period. *Risk* brings attention to the assessment of the potential for exacerbations, adverse effects caused by medications, and disease progression. Exacerbations have been assessed over the past year to determine seasonal patterns and the risk for future exacerbations, as summarized in Fig 2 from EPR-3.¹

From the Breathing Institute and Pulmonary Medicine Section, Children's Hospital Colorado and University of Colorado School of Medicine.

Disclosure of potential conflict of interest: S. J. Szeffler has consulted for Aerocrine, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Genentech, Novartis, Roche, and Teva and has received research support from the National Institutes of Health; the National Heart, Lung, and Blood Institute; GlaxoSmithKline; and the Colorado Cancer, Cardiovascular, and Pulmonary Disease Program. He is also a former member of the Global Initiative for Asthma Scientific Committee and the National Asthma Education and Prevention Program Expert Panel 3.

Received for publication December 20, 2017; revised March 12, 2018; accepted for publication March 23, 2018.

Available online April 5, 2018.

Corresponding author: Stanley J. Szeffler, MD, The Breathing Institute, Section of Pulmonary Medicine, Children's Hospital Colorado, 13123 E 16th Ave, Box B395, Aurora, CO 80045. E-mail: Stanley.Szeffler@childrenscolorado.org.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2018.03.010>

Abbreviations used

CASI: Composite Asthma Severity Index
 COPD: Chronic obstructive pulmonary disease
 EPR-3: Expert Panel Report 3
 GINA: Global Initiative for Asthma
 ICAC: Inner-City Asthma Consortium
 ICS: Inhaled corticosteroid
 NAEPP: National Asthma Education and Prevention Program
 NHLBI: National Heart, Lung, and Blood Institute
 NIAID: National Institute for Allergy and Infectious Diseases
 NICE: National Institute for Health and Care Excellence
 NIH: National Institutes of Health
 SAEPI: Seasonal Asthma Exacerbation Prediction Index

Asthma treatment is organized in a step-care fashion to decrease impairment, minimize risk, and provide a decision path to achieve control. It begins with as-needed albuterol and continues in steps with increasing doses of inhaled corticosteroids (ICSs) and addition of additional medications until control is achieved. With each step, the guidelines list a preferred medication choice and alternatives.

ONGOING CHANGES AFFECTING ASTHMA CARE

Since the last update of the NAEPP asthma guidelines in 2007,¹ there have been several key National Heart, Lung, and Blood Institute (NHLBI) and National Institute for Allergy and Infectious Diseases (NIAID) studies that will be discussed in this review that should be considered in the next update to the asthma guidelines. Topics selected for update include systematic review of intermittent ICSs and long-acting muscarinic antagonists for asthma, clinical utility of fraction of exhaled nitric oxide measurement in asthma management, effectiveness of indoor allergen reduction and the role of bronchial thermoplasty in asthma management, and the role of immunotherapy in asthma treatment.³ It is not clear whether additional revisions will be made to the asthma guidelines beyond these selected topics.

Two other forms of asthma management guidance, the Global Initiative for Asthma (GINA) and the National Institute for Health and Care Excellence (NICE), focus on primary care for asthma.^{4,5} The GINA strategy is revised annually, is available as management guidance for countries to use in designing their own country-specific guidelines, and will undergo a total revision in the coming year. The focus of GINA has been on primary care clinicians to increase the standard of care, especially in developing countries. GINA also considers the economic and resource limitations of underdeveloped countries in proposing its strategies. It is still very important to make the appropriate diagnosis so that treatment can be started and to provide guidance on treatment choices in patients with mild-to-moderate asthma. However, certain details of this strategy cannot be used in all countries because of differences in regulatory approval and cost considerations. For example, the recommended application of maintenance and an as-needed ICS/long-acting β -adrenergic agonist strategy included in GINA is not approved in the United States. NICE in the United Kingdom is focused on mild-to-moderate asthma and primary care physicians.⁵ Interestingly, the most recent version of NICE strongly encouraged use of

spirometry and exhaled nitric oxide measurement in asthma management.

The challenge for GINA and NICE in updating these strategies and for countries in developing their own guidelines is how to handle this rapidly evolving literature to integrate new information in a timely fashion. Each piece of guidance must also address the core needs of the health-disparate population while also identifying those who are not responding to advanced treatment strategies.

LONG-TERM EFFECT OF ASTHMA

There is growing concern regarding the long-term outcomes of early and poorly controlled childhood asthma on resultant irreversible pulmonary function.⁶⁻¹¹ These observations should prompt a practice change to identify patients at risk for adverse respiratory outcomes of childhood asthma, to monitor disease progression, and to design intervention strategies that could either prevent or reverse asthma progression in children. We also have the opportunity to implement a more personalized or individualized approach to asthma care at all levels of severity and in all age groups, including the elderly.

TOOLS TO USE IN THE COMING YEARS

The next paradigm shift should focus on addressing the risk domain, namely preventing asthma exacerbations and disease progression, including lung function loss and adverse effects of medications. Attention should continue to be directed toward minimizing both risk and impairment with a goal of achieving optimal control. Based on several NIH studies conducted over the last 10 years, we now have the tools necessary to accomplish this goal. The tools include assessment of lung function over time or defining trajectories of lung growth, CASI, a panel of useful biomarkers, SAEPI, and rapidly advancing technology that includes adherence monitoring.

Lung function trajectories

Recent reports on long-term studies have shown that asthma has the potential to lead to persistent and severe loss in lung function over time.⁶⁻⁹ The varying patterns of lung function development over time in children with persistent asthma were depicted by McGeachie et al¹¹ from 20 years of follow-up in the NHLBI's Childhood Asthma Management Program.¹⁰ Spirometry was measured at least annually, and 4 distinct patterns of lung function over time were described. Two patterns included reduced lung growth from early childhood, and 2 patterns displayed evidence of early decrease in pulmonary function after age 20 years (Fig 3).¹¹ Approximately 11% of those participants met the physiologic criteria for advanced levels of COPD in early adulthood. Alternatively, this might be the type of pattern that is currently referred to as asthma-COPD overlap.¹² Based on these observations, children with persistent asthma should have ongoing measures of lung function to classify their trajectory of lung growth/phenotype and use it to consider a potential intervention strategy, such as trigger avoidance, assessment of medication adherence, increased caregiver/provider communication, assistance with medication administration in the school setting, smoking cessation, smoking avoidance, home assessment, career counseling, reversibility testing with conventional

Evolving Patterns in Asthma Management

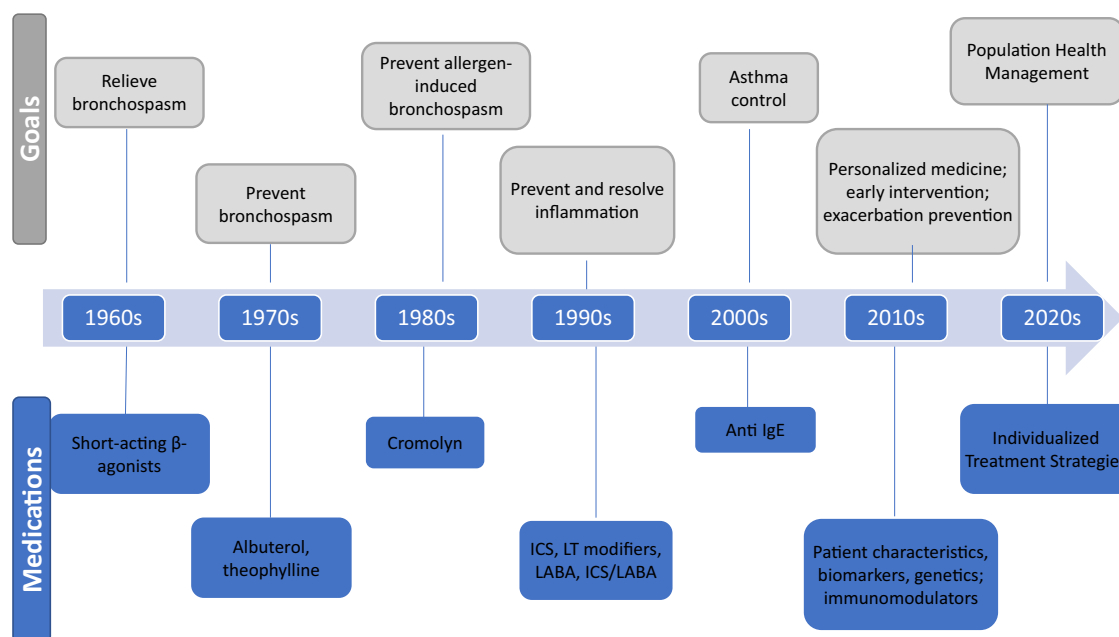


FIG 1. Summary of changes in asthma management that integrate the focus of disease activity and the corresponding medications developed to address this therapeutic target. LABA, Long-acting β -agonist.

therapy, and a clinical trial of immunomodulator therapy to assess response. The recommendations for avoiding smoking and environmental assessment and control are the types of measures that should be recommended for all patients with asthma based on their severity level.¹³ In addition to optimal asthma management, access to care, and affordable medications, patients should be cautioned against potential harmful effects of vaping, fracking, chemical exposures, and climate change based on their individual living conditions and susceptibilities.

CASI

CASI was developed by the NIAID Inner-City Asthma Consortium (ICAC) as a composite outcome measure to assess the effect of anti-IgE intervention in study participants aged 12 to 20 years.¹⁴ This index contains all of the key components in the impairment and risk domains, including daytime and nighttime symptoms, pulmonary function, treatment step, and number of exacerbations, and is the best measure currently available for overall asthma burden. The CASI score correlates with levels of asthma severity, and in a recent study, Krouse et al¹⁵ defined minimal important difference values. It is available free of charge at www.asthmaseverity.org. CASI has many other advantages for population health management, such as identifying and classifying patients requiring further evaluation, assessing the effect of an intervention, prompting step-down therapy based on follow-up of the score and individual components over time, and evaluating an overall population of asthma severity to name a few. One limitation is that it does not include scoring for oral corticosteroids, tiotropium, and immunomodulators, such as omalizumab. It will require periodic updates to account for new

medications and formulations and also to consider application in adults, especially those with severe asthma receiving daily oral corticosteroids.

Biomarker panel

The NIH Asthma Outcomes Task Force identified a set of biomarkers that should be considered in developing NIH-funded asthma research.¹⁶ These biomarkers include a panel to assess allergen sensitization as a core biomarker for characterization and supplementary biomarkers, including blood and sputum eosinophil counts, exhaled nitric oxide values, and total serum IgE levels, for addressing specific questions. In subsequent studies funded by NIH asthma networks, these biomarkers proved useful in identifying young children who respond best to daily ICSs and older children who have a more favorable response to ICSs over leukotriene receptor antagonists.¹⁷⁻¹⁹ These biomarkers have also been applied in decisions around the use of immunomodulator therapy in patients with severe asthma and even predicting likelihood of response. For example, sputum and blood eosinophil counts have been useful in identifying patients more likely to respond to immunomodulatory therapy, including anti-IgE and anti-IL-5 therapy.^{20,21}

Preventing seasonal exacerbations

Current therapy will likely reduce the risk of an asthma exacerbation in most but not all patients. SAEPI was developed and validated by the NIAID ICAC to identify children at risk for an asthma exacerbation.^{22,23} An exacerbation in the prior season and low pulmonary function are predictors of an asthma

BOX 4-1. SAMPLE RECORD FOR MONITORING THE RISK DOMAIN IN CHILDREN: RISK OF ASTHMA PROGRESSION (INCREASED EXACERBATIONS OR NEED FOR DAILY MEDICATION, OR LOSS OF LUNG FUNCTION), AND POTENTIAL ADVERSE EFFECTS OF CORTICOSTEROID THERAPY

Patient name:					
Date					
Long-term control medication					
ICS daily dose*					
LTRA					
LABA					
Theophylline					
Other					
Significant exacerbations					
Exacerbations (number/month)					
Oral systemic corticosteroids (number/year)*					
Hospitalization (number/year)					
Pulmonary function					
Prebronchodilator FEV ₁ /FVC					
Prebronchodilator FEV ₁ percent predicted					
Postbronchodilator FEV ₁ percent predicted					
Percent bronchodilator reversibility					
Potential risk of adverse corticosteroid effects (as indicated by corticosteroid dose and duration of treatment)					
Height, cm					
Percentile					
Plots of growth velocity					

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LTRA, leukotriene receptor antagonist

*Consider ophthalmologic exam and bone density measurement in children using high doses of ICS or multiple courses of oral corticosteroids.

FIG 2. This table was developed as part of the NAEPP EPR-3 and is designed to aid the clinician in summarizing components of the risk domain to follow these elements over time. This type of table could now be expanded and integrated into electronic medical records to provide a comprehensive picture of the natural history of asthma in an individual patient. It could also be modified to include a panel of biomarkers that would be obtained periodically.

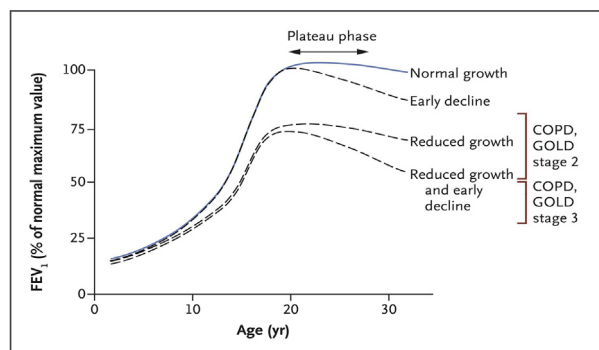
exacerbation at any time of the year, whereas measures like increased numbers of positive allergen skin test responses, increased ICS doses, increased exhaled nitric oxide levels, and increased blood eosinophil counts and total and specific IgE levels might be useful for predicting a seasonal asthma exacerbation, especially during the fall season.²² The Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations (PROSE) study demonstrated that in the most challenging patients, who are already at a high treatment step or had a recent asthma exacerbation, a short course of anti-IgE administered just before and during the fall season (ie, the early part of the school year) can reduce the risk of a fall asthma exacerbation.²⁴

Adherence monitoring

It is important to emphasize education for patients and parents to achieve better adherence to the management plan. Poor technique around medication administration remains an important problem.²⁵ Poor education and adherence are associated with increased morbidity and increased risk for mortality in asthmatic patients. Although one can easily

obtain information from pharmacies regarding the number of prescription refills for a patient, technology is rapidly advancing and will eventually affect asthma care in identifying patients whose adherence deteriorates over time.²⁶⁻²⁸ Electronic adherence monitoring techniques are now available to monitor day-to-day rescue and long-term controller therapy.²⁸ Applying this technology can identify patients with inconsistent adherence or those with breakthrough symptoms. Successful adoption of the technology requires a monitoring system and appropriate support strategies to enhance adherence in those at risk for an asthma exacerbation. Currently, it incurs additional costs, but some project that electronic monitoring features will become part of future medication dispensing. Application of these tools on a wider scale will not only improve adherence but also identify adherence phenotypes. Adherence monitoring can also lead to new strategies to support adherence to the medication schedule and a reduction in medication use for those with well-controlled symptoms or to justify the use of advanced therapies, such as an immunomodulator that can incur higher costs for those whose symptoms remain inadequately controlled despite optimal conventional therapy and adherence.

Longitudinal Lung-Function Trajectories



McGeachie MJ et al. N Engl J Med 2016;374:1842-1852



FIG 3. This figure is reprinted from McGeachie et al¹¹ with permission. It depicts the lung function trajectories during the first 3 decades of life as the percentage of maximum FEV₁ as modeled from data in the Childhood Asthma Management Program continuation studies. GOLD, Global Initiative for Chronic Obstructive Lung Disease.

INTRODUCING NEW MEDICATIONS AND STRATEGIES

Neither NICE, GINA, nor the 2007 NAEPP EPR-3 guidelines currently address the complex questions now being raised by asthma specialists in managing severe asthma and asthma across the lifespan. Each year, the *Journal* has summarized key literature related to advances in asthma research.²⁹ In the past 2 years, a number of new medications and strategies have been added to our armamentarium for asthma management, including tiotropium; biologics, such as omalizumab and anti-IL-5 agents (mepolizumab, reslizumab, and benralizumab); and bronchial thermoplasty, with varying levels of approval for use in children along with several other medications, such as anti-IL-4/IL-13 (dupilumab) and perhaps anti-thymic stromal lymphopoietin, that await approval for asthma.²⁹⁻³¹

WHERE DO WE GO FROM HERE?

It is exciting to see a number of useful tools for managing asthma but discouraging to see that they are not readily applied. At this time, these tools could be applied in specialty care and subsequently in primary care after a suitable implementation and validation period. Applying these tools could change the dialogue between the asthma specialist, primary care physician, patient, and parent and shift the paradigm from a reactive management strategy to a prevention strategy. Risk monitoring, as proposed in [Fig 4](#), can be used to more completely assess the risk for exacerbations and monitor progression of asthma to further reduce asthma burden. With the rapid advancement in technology and introduction of new medications and new biomarkers, we will be able to move toward a biomarker-directed treatment plan and technology-oriented monitoring.

Develop a care plan across the lifespan

To manage asthma from the “cradle to the rocker” more effectively, it is important to assess lung function over time to define a lung trajectory, as presented in the report by McGeachie et al,¹¹ such as that defined in [Fig 3](#). At less than 16 years of age,

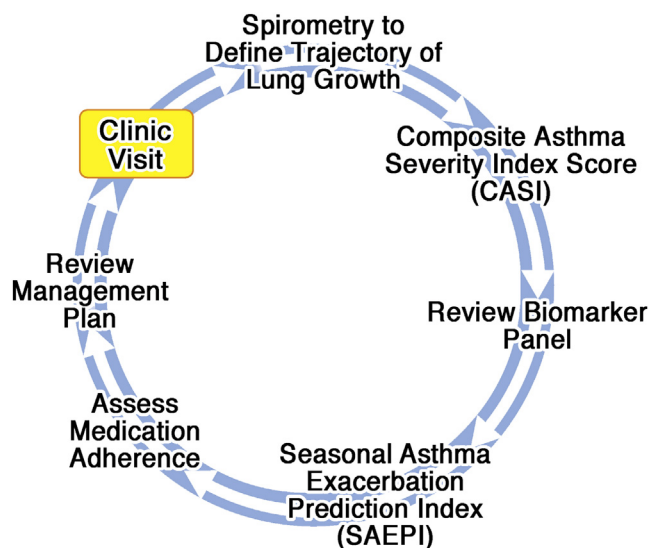


FIG 4. A model for conducting a clinic visit for asthma that assesses and monitors the risk domain and then integrates that information with other portions of the patient record. Information derived from assessing the social determinants of health could be used to direct the patient and family to community resource support.

measurements obtained annually can define a pattern of reduced lung growth characterized by a prebronchodilator FEV₁ consistently less than the 25th percentile or less than -1.67 when using a reported z score, as defined by the recent Global Lung Initiative.³² After age 16 years, a plateau in these measurements is likely to occur, and after about age 25 years, one can assess a decrease in lung function, again based on either prebronchodilator FEV₁ percentile or z score. This lung trajectory information could then be reported in electronic medical records in a pictorial fashion, and these reports could be included subsequently in interpretations of spirometric data. This would prompt primary care physicians to include this information in monitoring and also serve as a reminder to obtain an annual measurement. If the primary care setting does not measure spirometry, asthma specialists could provide this assessment by creating asthma hubs.⁵

With this information, the clinician can then determine the effect of an intervention, such as smoking cessation, a course of systemic steroid therapy, or an immunomodulator. Reviewing these data with a parent or a patient of older age, including adolescents, would change the dialogue and engage them in looking at long-term outcomes based on the current trajectory of lung growth and future projection similar to the dialogue generated in discussing linear growth with height measurements or potential obesity implications from weight measurements.

Addition of CASI monitoring over time to these trajectories of lung growth would also provide a picture of changing asthma burden over time. An increasing CASI score could point to a review of the management plan and prompt consideration for alternative approaches to management.

Identifying biomarkers and biologics to alter the course of asthma

Several years ago, Drs Erika von Mutius and Jeffrey Drazen³³ provided a commentary on asthma over the years spanning 1828

to 2012 and concluded that asthma as a disease has not changed for 2 centuries. Although some advances have been made in the diagnosis, monitoring, and understanding of airway inflammation, the precise nature of that inflammation remains a mystery. We now have some useful biomarkers, such as the presence of eosinophils, IgE, and nitric oxide and indicators of specific allergy sensitization, that help us understand at least some of the driving forces present in asthmatic patients. As previously indicated, this set of biomarkers has proved useful in selecting initial step therapy in infants and children and, combined with the presence of patient characteristics, such as eczema and race/ethnicity, can help determine next-step therapy if there is an inadequate response to low-dose ICSs.^{17-19,34-36}

The challenge will now be to identify new biomarkers that can prove even better than the ones we now have available. Perhaps this will come from a systems biology approach that uses the various “omics” techniques combined with careful phenotyping of patients.³⁷ Those biomarkers should be cost-effective, readily available, and useful in not only assessing potential benefit from available biologic therapies but also leading to the discovery of new biologics. NIH asthma networks, including ongoing work in the NIAID ICAC and the new NHLBI Precision Interventions for Severe and/or Exacerbation Prone Asthma (PrecISE) Network, will conduct studies to identify new biomarkers and provide insight into biomarker-directed therapy. It is also a hope that some of these biomarkers and biologics could be useful in managing the early stages of asthma and altering the natural history of the disease.

Individualizing the strategy for the care setting

In addition, use of biomarkers and patients’ characteristics to individualize therapy, the role of the home environment, and socioeconomic conditions are other parameters to consider in designing treatment regimens. We are just beginning to understand the effect of the urban versus rural environment on asthma airway inflammation, progression, and long-term outcomes. We know that patients in both settings face similar problems related to poor access to care, home environment, and outdoor air quality. However, there are differences in the components. Access to care in the inner city might be related to inconsistent care, whereas access to care in rural communities might be related to a shortage of clinicians in the area, especially asthma specialists. Indoor air in the inner city can consist of exposure to smoke infiltration from neighboring units, rodents, insects, and mold, whereas that in the rural setting can be related to heating techniques, farm animal exposure, and crop procedures. Outdoor air in the inner city can be affected by trapped air vents, traffic exposure, and manufacturing, whereas outdoor air in the farm area can be related to harvesting, blowing dust exposure, and climate changes. The relative contribution of T2-high and T2-low classifications could vary in each setting and influence the response to various interventions. The T2 factors are generally considered to be mediators and cell types associated with allergic inflammation, such as IgE levels, eosinophil counts, periostin levels, and exhaled nitric oxide levels.

Understanding the effects of social determinants of health, such as stress, access to food and shelter, and continuity in health care, on asthma will provide novel strategies for supporting children in inner-city and rural environments, especially those affected by

access to care or educational opportunities.³⁸⁻⁴¹ For example, hospitals and clinics can organize resources to provide access to food or transportation, there might be more extensive use and training of health navigators to support care, schools can serve as a source of asthma education and medication administration along with monitoring care, and technology can be used to monitor medication adherence, assess variation in physiology, and conduct visits from a distance by means of telemedicine.⁴²⁻⁴⁵ Telemedicine can also be used to provide access to specialist care for those with poorly controlled asthma.⁴⁶ For adults, community settings and collaboration between patients, primary care clinicians, specialists, and public health representatives might be part of a population health management strategy. Studies to evaluate the effects of these programs will need to include patient-centered outcomes in the assessment of response to interventions and shared decision making.⁴⁵

Future directions for asthma guidelines

GINA has transitioned to serving as an asthma strategy rather than a guideline. Currently, GINA emphasizes an evidence-based approach with strong requirements for making modifications to customize patient care. Although this can be a benefit for standardizing care, it might limit progress and advancement in care. Expert panels for asthma guidelines face the challenge of integrating a rapidly developing and complex literature when it comes to the number of new medications being introduced along with potential biomarkers and patients’ clinical and social characteristics, which could be used in individualizing an approach. One approach is to use composite publications to update key areas and advance the field for asthma specialists.⁴⁷ This has the advantage of addressing key issues, summarizing information in an expedited way, and transferring information in a timely fashion.

Perhaps one consideration for all asthma guidelines might be to develop a core piece focused on the management of mild-to-moderate asthma that includes consideration for developing countries, such as that recently presented by NICE,⁵ and include additional sections for difficult-to-treat asthma. Promoting a standard approach to care that will help identify those not responding appropriately could be included in a severe asthma section. These sections would be focused on difficult-to-treat or treatment-resistant asthma, which is usually managed by asthma specialists. The section on patients with difficult-to-treat asthma could include evaluation, such as medication adherence, specific social determinants, and specialist evaluation for other diseases. This approach would inform treatment by the respective health care system and could be used to justify decisions around advanced care, such as nonconventional strategies or immunomodulator therapy.

Country-specific guidelines could then use this framework to highlight areas of consistency and address health care, environmental, and medication access issues pertinent to the individual country. For example, some countries have one uniform health care system in which such a strategy could be applied uniformly, whereas other countries have multiple health care services, such as the United States, where a health care system-specific modification would be applied to clarify what is and is not available. This is particularly important for severe asthma and the use of costly medications in which a careful evaluation, as well as cost considerations, should be transparent.

Hopefully, such an effort would lead eventually to a worldwide harmonization of treatment and a more global approach to asthma management.

Based on this review, future guidelines should incorporate recommendations to follow spirometry over time and define trajectories of lung growth to assess risk for reduced lung growth and early decline, asthma burden, appropriate use of biomarkers in selecting and monitoring therapy, incorporation of social determinants, assessment of risk for seasonal exacerbations, and consideration of adherence monitoring for difficult-to-manage asthma (Fig 4). Guidelines should include a core dedicated to the diagnosis and treatment of intermittent and mild and moderate persistent asthma and additional sections dedicated to the identification of severe asthma and treatment recommendations. The goal of this approach is a reduction in asthma exacerbations along with reduced asthma morbidity.

I thank Monica Federico who provided a detailed review of the presentation, along with Heather Hoch, William Anderson, Arthur McFarlane, Mark Brown, Andrew Liu, and Robin Deterding from the Breathing Institute and international reviewers, including Ana Maria Herrera Gana (Santiago, Chile) and Soren Pedersen (Copenhagen, Denmark). I also acknowledge the very thoughtful comments of Zuhair Ballas, Editor-in-Chief of the *Journal of Allergy and Clinical Immunology*, along with the *Journal* reviewers. In particular, I thank the participants, parents, research staff, and colleagues who participated in the studies mentioned in this rostrum.

REFERENCES

- National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
- Zahran HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital signs: asthma in children—United States, 2001-2016. *MMWR Morb Mortal Wkly Rep* 2018;67:149-55.
- National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group. Draft needs assessment report for potential update of the Expert Panel Report-3(2007): guidelines for the diagnosis and management of asthma, April 2014. 2014. Available at: <https://www.nhlbi.nih.gov/files/docs/resources/lung/NHLBAC-Asthma-WG-Report.pdf>. Accessed February 3, 2018.
- Global Initiative for Asthma. Global strategy for asthma management and prevention, 2017. Available at: <http://www.ginasthma.org/>. Accessed December 2, 2017.
- National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. Available at: <https://www.nice.org.uk/guidance/NG80/evidence>. Accessed December 2, 2017.
- Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.
- Tai A, Tran H, Roberts M, Clarke N, Gibson AM, Vidmar S, et al. Outcomes of childhood asthma to the age of 50 years. *J Allergy Clin Immunol* 2014;133:1572-8.
- Berry CE, Billheimer D, Jenkins IC, Lu ZJ, Stern DA, Gerald LB, et al. A distinct low lung function trajectory from childhood to the fourth decade of life. *Am J Respir Crit Care Med* 2016;194:607-12.
- Tagiveya N, Devereux G, Fielding S, Turner S, Douglas G. Outcomes of childhood asthma and wheezy bronchitis. *Am J Respir Crit Care Med* 2016;193:23-30.
- The Childhood Asthma Management Program Research Group. Long term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
- McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842-52.
- Reddel HK. Treatment of overlapping asthma-chronic obstructive pulmonary disease: can guidelines contribute in an evidence-free zone? *J Allergy Clin Immunol* 2015;136:546-52.
- Gold DR, Adamkiewicz G, Arshad SH, Celedón JC, Chapman MD, Chew GL, et al. NIAID, NIEHS, NHLBI, and MCAN Workshop Report: the indoor environment and childhood asthma—implications for home environmental intervention in asthma prevention and management. *J Allergy Clin Immunol* 2017;140:933-49.
- Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, et al. Development and validation of the composite asthma severity index—an outcome measure for use in children and adolescents. *J Allergy Clin Immunol* 2012;129:694-701.
- Krouse RZ, Sorkness CA, Wildfire JJ, Calatroni A, Gruchalla R, Hershey GKK, et al. Minimally important differences and risk levels for the Composite Asthma Severity Index. *J Allergy Clin Immunol* 2017;139:1052-5.
- Szefer SJ, Wenzel S, Brown R, Erzurum SC, Fahy JV, Hamilton RG, et al. Asthma outcomes: biomarkers. *J Allergy Clin Immunol* 2012;129(suppl):S9-23.
- Szefer SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Clin Allergy Immunol* 2005;115:233-42.
- Zeiger RS, Szefer SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, et al. Response profiles to fluticasone and montelukast in mild to moderate persistent childhood asthma. *J Allergy Clin Immunol* 2006;117:45-52.
- Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehand WJ, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138:1608-18.
- Hanania NA, Wenzel S, Rosen K, Hsieh H-J, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
- Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
- Teach SJ, Gergen PJ, Szefer SJ, Mitchell HE, Calatroni A, Wildfire J, et al. Seasonal risk factors for asthma exacerbations among inner city children. *J Allergy Clin Immunol* 2015;135:1465-73.
- Hoch HE, Calatroni A, West JB, Liu AH, Gergen PJ, Gruchalla RS, et al. Can we predict fall asthma exacerbations? Validation of the seasonal asthma exacerbation index. *J Allergy Clin Immunol* 2017;140:1130-7.
- Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136:1476-85.
- Sanchis J, Gich I, Pedersen S. Aerosol Drug Management Improvement Team (ADMIT). Systematic review of errors in inhaler use: has patient technique improved over time? *Chest* 2016;150:394-406.
- Krishnan JA, Bender BG, Wamboldt FS, Szefer SJ, Adkinson NF, Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol* 2012;129:112-8.
- Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol* 2014;134:1260-8.
- Merchant RK, Inamdar R, Quade RC. Effectiveness of population health management using the Propeller Health Asthma Platform: a randomized clinical trial. *J Allergy Clin Immunol Pract* 2016;4:455-63.
- Anderson WC, Apter A, Dutmer CM, Searing DA, Szefer SJ. Advances in asthma in 2016: designing individualized approaches to management. *J Allergy Clin Immunol* 2017;140:671-80.
- Szefer SJ, Chmiel JF, Fitzpatrick AM, Giacomia G, Green TP, Jackson DJ, et al. Asthma across the ages: knowledge gaps in childhood asthma. *J Allergy Clin Immunol* 2014;133:3-13.
- Anderson WC 3rd, Szefer SJ. New and future strategies to improve asthma control in children. *J Allergy Clin Immunol* 2015;136:848-59.
- Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324-43.
- Von Mutius E, Drazen JM. A patient with asthma seeks medical advice in 1828, 1928 and 2012. *N Engl J Med* 2012;366:827-34.
- Spahn J, Malka J, Szefer SJ. Current application of exhaled nitric oxide in clinical practice. *J Allergy Clin Immunol* 2016;138:1296-8.
- Lemanske R, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma while receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
- Malka J, Mauger DT, Covar R, Rabinovitch N, Lemanske RF, Spahn JD, et al. Eczema and race as combined determinants for differential response to step-up asthma therapy. *J Allergy Clin Immunol* 2014;134:483-5.
- Nkrumah-Elie Y, Elie M, Reisdorph N. Systems biology approaches in asthma management. In: Szefer SJ, Holguin F, Wechsler M, editors. Future directions for personalized medicine for asthma for the clinician. St Louis: Elsevier; 2018. pp. 151-60.

38. Schulz A, Northridge ME. Social determinants of health: implications for environmental health promotion. *Health Educ Behav* 2004;31:455-71.
39. Garg A, Butz AM, Dworkin PH, Lewis RA, Thompson RE, Serwint JR. Improving the management of family psychosocial problems at low-income children's well-child care visits: The WE CARE Project. *Pediatrics* 2007;120:547-58.
40. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics* 2009;123(suppl):S174-84.
41. Woods ER, Bhaumik U, Sommer SJ, Chan E, Tsopelas L, Flegler EW, et al. Community asthma initiatives to improve health outcomes and reduce disparities among children with asthma. *MMWR Morb Mortal Wkly Rep* 2016;65:11-20.
42. Kerckmar C, Beck AF, Sauers-Ford H, Simmons J, Wiener B, Crosby L, et al. Association of an asthma improvement collaborative with health care utilization in Medicaid-insured pediatric patients in an urban community. *JAMA Pediatr* 2017;171:1072-80.
43. Liptzin DR, Gleason MC, Cicutto LC, Cleveland CL, Shocks DJ, White MK, et al. Developing, implementing, and evaluating a school-centered asthma program: Step Up Asthma Program. *J Allergy Clin Immunol Pract* 2016;4:972-9.
44. Lemanske RF, Kakumanu S, Shanovich K, Antos N, Cloutier MM, Mazyck D, et al. Creation and implementation of SAMPRO™: a school-based asthma management program. *J Allergy Clin Immunol* 2016;138:711-23.
45. Anise A, Hasnain-Wynia R. Patient-centered outcomes research to improve asthma outcomes. *J Allergy Clin Immunol* 2016;138:1503-10.
46. Halterman JS, Fagnano M, Tajon RS, Tremblay P, Wang H, Butz A, et al. Effect of the school-based telemedicine enhanced asthma management (SB-TEAM) program on asthma morbidity: a randomized clinical trial. *JAMA Pediatr* 2018; 172:e174938.
47. Szefer SJ, Holguin F, Wechsler M. Future directions for personalized medicine for asthma for the clinician. In: Szefer SJ, Holguin F, Wechsler M, editors. *Personalizing asthma management for the clinician*. St Louis: Elsevier; 2018.