

Advances in pediatric asthma in 2012: Moving toward asthma prevention

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Last year's "Advances in pediatric asthma: moving forward" concluded the following: "Now is also the time to utilize information recorded in electronic medical records to develop innovative disease management plans that will track asthma over time and enable timely decisions on interventions in order to maintain control that can lead to disease remission and prevention." This year's summary will focus on recent advances in pediatric asthma on modifying disease activity, preventing asthma exacerbations, managing severe asthma, and risk factors for predicting and managing early asthma, as indicated in *Journal of Allergy and Clinical Immunology* publications in 2012. Recent reports continue to shed light on methods to improve asthma management through steps to assess disease activity, tools to standardize outcome measures in asthma, genetic markers that predict risk for asthma and appropriate treatment, and interventions that alter the early presentation of asthma to prevent progression. We are well on our way to creating a pathway around wellness in asthma care and also to use new tools to predict the risk for asthma and take steps to not only prevent asthma exacerbations but also to prevent the early manifestations of the disease and thus prevent its evolution to severe asthma. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

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Journal publications in 2011 and 2012 serve as a base for evaluating the current status of asthma and set the stage for looking to

Abbreviations used

FENO: Fraction of exhaled nitric oxide
HRV: Human rhinovirus
ICS: Inhaled corticosteroid
LABA: Long-acting β -adrenergic agonist
RSV: Respiratory syncytial virus
SNP: Single nuclear polymorphism
Treg: Regulatory T
TSLP: Thymic stromal lymphopoietin

the future direction of asthma management. Last year's "Advances in pediatric asthma in 2011: moving forward" included a discussion of studies related to accomplishments in asthma care, new information to supplement the asthma guidelines, and insights that could affect future management.¹ Last year's review by Andrea Apter² on adult asthma focused on ways to improve health outcomes by understanding mechanisms of disease, environmental exposures, and new management principles.

A series of *Journal* reviews, entitled "Asthma: current status and future directions" profiled major issues in asthma.³⁻⁹ Dr Jeffrey Drazen, Editor-in-Chief of the *New England Journal of Medicine*, ended the series with an editorial entitled "Asthma: the paradox of heterogeneity." He stated that what we need to do is make progress in understanding the root causes of asthma. For this, we need targeted diagnostics and therapeutics so we can infer causality and design the best treatment for each patient.¹⁰ In addition, Barnett and Nurmagambetov¹¹ provided a cost analysis of asthma in the United States.

Currently, it is recognized that inhaled corticosteroids (ICSs) are very effective in reducing the risk of asthma exacerbations and that the combination of long-acting β -adrenergic agonists (LABA) and ICSs, both as maintenance and also as rescue therapy, has a significant further beneficial effect on reducing exacerbations and maintaining asthma control.¹² In addition, leukotriene receptor antagonists, omalizumab, sputum eosinophil-adjusted therapy, and anti-IL-5 in patients with sputum eosinophilia can also be used to reduce the risk of an asthma exacerbation.¹²

Better organization of overall asthma care can be used to improve asthma outcomes in large health care systems.¹³ Advances in genetic discoveries will help identify patients at risk for asthma and for the development of certain phenotypes of asthma.^{14,15} The availability of such tools should lead to a proactive preventative approach to asthma care.

This review will highlight 2012 *Journal* publications that provide new information to identify risk factors for the development of asthma, assess disease activity, prevent asthma exacerbations, and manage severe asthma. Important theme issues in the *Journal* included air pollution, infection, early asthma, and genetics.

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ANALYZING DISEASE ACTIVITY

Indicators of disease activity

Gershon et al¹⁶ set out to examine the course of asthma activity in a population study. They noted that over 15 years, most patients with asthma had active disease that was interspersed with periods of inactivity when they did not require medical attention and were likely in remission. This study should prompt further studies that facilitate prognostication of the course of disease to permit a proactive management approach for patients.

Biologic markers

It would be useful to complement clinical history, spirometry, and measurement of biologic markers to enhance the evaluation of disease activity. One biomarker that has received attention is exhaled nitric oxide. Fuchs et al¹⁷ reported that children living on farms are protected against wheeze independently of atopy and that there was no farm effect on lung function and fraction of exhaled nitric oxide (FENO). Patelis et al¹⁸ studied the IgE antibody profile for a broad spectrum of allergen molecules in asthmatic patients and concluded that FENO, bronchial hyperresponsiveness, and the risk of asthma increase with multiple sensitizations to different allergen groups. In addition, IgE antibodies against food allergens are independently associated with increased FENO levels and increased risk of asthma with simultaneous sensitization to pollen allergens. Gouvis-Echraghi et al¹⁹ reported that in young children FENO values appear to be influenced by poor asthma control and disease severity and then by atopic features.

Jia et al²⁰ reported that periostin is a systemic biomarker of airway eosinophilia in asthmatic patients and has potential utility in patient selection for emerging asthma therapies targeting T_H2 inflammation. Nair and Kraft²¹ comment that a simple blood test would be ideal and potentially clinically very useful. Periostin shows some promise, particularly in patients with severe asthma, but must be further evaluated.

Another promising area of investigation is the area of genetics and epigenetics. Ji and Khurana Hershey²² summarized recent findings on the genetic and epigenetic regulation of responses to ambient air pollutants, specifically respirable particulate matter, and their association with the development of allergic disorders. Understanding epigenetic markers and how they integrate with genetic influences to translate the biologic effect of particulate exposure could be critical to developing novel preventative and therapeutic strategies for allergic disorders. Furthermore, epigenetic mechanisms provide a promising line of inquiry that might, in part, explain the inheritance and immunobiology of asthma.²³ Hawkins et al²⁴ reported that the IL-6 receptor (*IL6R*)-coding single nucleotide polymorphism (SNP) rs2228145 (Asp³⁵⁸ Ala) could have a pathologic role in the airways that could identify subjects at risk for severe asthma. With anti-IL-6 receptor therapies that block IL-6 transsignaling, there might be a therapeutic value for this treatment in patients with severe asthma. Tantisira et al²⁵ identified the T gene as a novel determinant of ICS pulmonary response using genome-wide association analysis.

Environment

Bauer et al²⁶ reviewed current knowledge on how air pollutants modify Toll-like receptor-dependent and nucleotide-binding oligomerization domain-like receptor-dependent signaling and

host defense responses in the lung to address the role of air pollutants on innate immunity. Hernandez et al²⁷ demonstrated that gene expression profiles in sputum cells from atopic asthmatic patients are distinctly different from those of healthy volunteers. Compared with healthy subjects, asthmatic patients showed increased immune signaling, increased proinflammatory cytokine levels, and upregulated expression of the v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (*ERBB2* [HER-2]) gene network on exposure to ozone.

Cakmak et al²⁸ reported an association between aeroallergens and hospitalizations for asthma, which was enhanced on days of higher air pollution. These observations suggest that minimizing exposure to air pollution might reduce allergic exacerbations of asthma. Laumbach and Kipen²⁹ reviewed the respiratory health effects of air pollution and concluded that air pollution from sources such as traffic and burning biomass fuels is a major preventable cause of increased incidence and exacerbations of respiratory disease. Leung et al³⁰ reviewed the role of pollution in the increasing prevalence and exacerbations of allergic disease in Asia. Interestingly, they found inconsistent evidence regarding the roles of individual pollutants in the initiation of asthma and allergy among Asian children and adults.

Ziska and Beggs³¹ reported that anthropogenic climate change and increasing atmospheric carbon dioxide concentrations have the potential to transform almost all spatial and temporal aspects of plant-based aeroallergen (production, allergenicity, and distribution), with subsequent effects on aeroallergen exposure and the severity and prevalence of allergic disease. Darrow et al³² examined short-term associations between ambient concentrations of various pollen taxa and emergency department visits for asthma and wheeze in Atlanta between 1993 and 2004. They noted that *Poaceae* and *Quercus* species pollen contribute to asthma morbidity in Atlanta. Indeed, the role for the allergist is important in providing appropriate information on environmental control measures that can effectively reduce asthma and allergy symptoms.³³

Rabinovitch et al³⁴ examined the health effects of concurrent environmental tobacco smoke and ambient particulate matter exposure in children with asthma. They concluded that concurrent tobacco smoke exposure limits the increase in urinary leukotriene E₄ levels and albuterol use in response to an increase in concentrations of ambient particulate matter up to 2.5 μ m in size. Baccarelli and Kaufman³⁵ commented on these findings and suggested that they raise new questions regarding our understanding of the environmental determinants of asthma. Li et al³⁶ and Ledford et al³⁷ provided commentaries on the public health benefits of air pollution control. The difficulty in formulating national policy is that all decisions will affect costs paid by industry or utilities and ultimately paid by the consumer and the public.

Vitamin D and asthma severity

Recently, attention has been directed to vitamin D and its role in asthma management. Several *Journal* publications explored potential cellular mechanisms for vitamin D. Du et al³⁸ reported on the association of variants of the class I MHC-restricted T cell-associated molecule gene (*CRTAM*) with asthma exacerbations and suggested that this association could be important for predicting patients at risk for exacerbations and a rationale for therapeutic intervention with vitamin D in a proportion of patients with high-risk asthma. Goleva et al³⁹ provided

information on the significant association between serum vitamin D status and steroid requirement and *in vitro* responsiveness to corticosteroids in children but, interestingly, not in adults. They suggested vitamin D supplementation might enhance corticosteroid responsiveness and control atopy and thereby improve asthma control in children.

Gupta et al⁴⁰ previously reported that children with steroid-resistant asthma have lower vitamin D levels compared with those seen in children with moderate asthma and control subjects. The serum vitamin D level was associated with lower lung function, poor asthma control, increased medication use, and asthma exacerbations.⁴⁰ This group also noted that higher vitamin D binding protein levels in bronchoalveolar lavage fluid in steroid-resistant asthmatic children than in nonasthmatic control subjects perhaps lead to airway inflammation.⁴¹ Chambers et al⁴² reported that the frequency of circulating forkhead box protein 3–positive CD4⁺ regulatory T (Treg) cells was significantly lower in steroid-resistant than in steroid-sensitive asthmatic patients with comparable disease severity. There was a strong functional correlation between vitamin D status, circulating forkhead box protein 3–positive CD4⁺ Treg cell numbers, and corticosteroid responsiveness. Tse et al⁴³ reported that vitamin D levels were associated with lower bone mineral density in children with asthma. Therefore children with high use of oral corticosteroids require vitamin D assessment and supplementation.

Asthma progression

Lopez-Guisa et al⁴⁴ have shown that airway epithelial cells from children with mild asthma exhibit greater expression of factors, including TGF- β , vascular endothelial growth factor, and periostin, associated with subepithelial airway remodeling than cells from atopic and healthy children. This is suggestive of an intrinsic dysregulation of the epithelial-mesenchymal trophic unit in patients with asthma.

O'Brian et al⁴⁵ reported that children with a history of recurrent severe wheezing exacerbations during the first 3 years of life had significantly lower lung function compared with that seen in children with no wheezing, mild-to-moderate wheezing only, and only 1 severe episode requiring systemic steroid therapy. Because baseline lung function was not available, it was not clear whether the exacerbations resulted in lower lung function or whether this might be a population at risk for exacerbations. Wu et al⁴⁶ studied the developmental patterns of asthma in children 3 to 11 years old. They noted that asthmatic children experienced patterns of disease remittance and relapse over time, and thus asthma should be followed over multiple time points. Brehm et al⁴⁷ reported that African ancestry is associated with reduced FEV₁ and forced vital capacity values in Puerto Rican children independently of indicators of socioeconomic status, health care access, and key environmental/lifestyle exposures. They concluded that these factors and the combination of African ancestry might influence lung development and growth during childhood.

Health outcome measures and systems management

Improvements in health care will come from collaborative efforts. As such, the International Collaboration of Asthma, Allergy and Immunology (iCAALL) was formed to address the increasing incidence of allergic diseases and asthma worldwide to

promote awareness, collaboration, and international recognition of allergy, asthma, and immunology.⁴⁸ One goal is to develop universal acceptance of evolving consensus documents to help create a bridge between primary care physicians and specialists. Tsai et al⁴⁹ investigated age-related differences in emergency department presentation and clinical outcomes for patients with acute asthma. They concluded that there is an urgent need for targeted interventions for older adults with asthma, especially with the aging US population.

The National Institutes of Health's Asthma Outcomes Task Force provided a report on the definition of asthma outcomes that should be used in conducting National Institutes of Health research.⁵⁰⁻⁵⁸ These outcome measures could be used in health outcomes assessment, as well as regulatory evaluation of new medications. One of the challenges in assessing asthma outcomes has been a methodological approach to measuring multiple factors together. Wildfire et al⁵⁹ provided the Composite Asthma Severity Index after its development and validation in the National Institutes of Allergy and Infectious Diseases Inner City Asthma Consortium. The Composite Asthma Severity Index has the ability to determine the level of asthma severity based on a composite clinical characterization of asthma that includes symptoms, lung function, exacerbations, and ongoing treatment.

Eakin et al⁶⁰ evaluated the effects of providing Breathmobile services versus a patient-physician communication intervention, both individually and together. They recommended that multi-level and multimodal strategies be developed to increase knowledge and motivation regarding the importance of routine asthma care. Rosas-Salazar et al⁶¹ identified health literacy as a factor contributing to poor health outcomes, including asthma. It is a key barrier to asthma knowledge. Long-term clinical trials are needed to assess the effect of interventions in subjects with asthma and low health literacy. This could lead to public initiatives to improve health care delivery.

Methods to improve asthma outcomes

Krishnan et al⁶² compared subjective and objective measurements of children's adherence to ICSs or placebo. They concluded that researchers should use objective rather than self-reported adherence data to identify clinical trial participants with low levels of adherence to study treatment. Goleva et al⁶³ studied the usefulness of peripheral blood cells in predicting steroid response in asthmatic patients. They concluded that a set of potential markers to predict response to oral corticosteroids could be helpful. Gelb et al⁶⁴ evaluated the role of exhaled nitric oxide on predicting the response to oral corticosteroids during an asthma exacerbation and did not find it to be clinically useful.

Prevention of asthma exacerbations

Zeiger et al⁶⁵ based on the findings of a cohort study of severe asthma, reported that prior exacerbations, short-acting β -agonist use, lung function, and the Asthma Therapy Assessment Questionnaire were independent predictors of exacerbations. This information supports the use of the impairment domain introduced in the Expert Panel Report 3 national guidelines to anticipate future exacerbations. Wu et al⁶⁶ noted that lung function can be used to predict hospitalizations, emergency department visits, and need for oral corticosteroid therapy in pediatric patients. It is also a good predictor of the effect of ICS therapy on the

probability of being hospitalized or experiencing urgent care visits. Rank et al⁶⁷ noted an increase in asthma controller/total medication ratio in a sample reflective of the US population was not associated with a decreased asthma exacerbation rate comparing 1997 with 1998 and 2004 with 2005. In addition, Colice et al⁶⁸ noted that patients with persistent and not well or poorly controlled asthma reported higher rates of acute care use, as well as emotional issues confirming that asthma management falls short of national asthma management targets. Therefore many patients need long-term controller therapy, and many who are receiving long-term controller therapy have symptoms that are not adequately controlled.

Bosco et al⁶⁹ identified pathways of the inflammatory network that are upregulated during virus-induced exacerbations. Interferon regulatory factor 7 (*IRF7*) was identified as a major hub connecting interferon-mediated antiviral responses. *IRF7* and associated innate signaling hubs are potential therapeutic targets for interventions. Of interest, Capili et al⁷⁰ reported that asthmatic patients are at increased risk of pertussis infection. A clinical implication of these findings is that targeting asthmatic patients for pertussis vaccination as a selective high-risk group might be appropriate.

Prior reports have indicated that ICSs reduce the frequency of exacerbations. Wells et al⁷¹ reported in adolescents and adults, including such high-risk subgroups as African American subjects and those with moderate-to-severe asthma, that treatment with ICS/LABA fixed-dose combination therapy appeared to perform as well as or better than ICS treatment alone in reducing severe asthma exacerbations. In a related report Brown et al⁷² reported on the long-term safety and efficacy of budesonide/formoterol in African American asthmatic adolescents and adults. This ICS/LABA combination was well tolerated over 12 months, with a safety profile similar to that of budesonide, whereas the exacerbation rate was reduced by 38% with combination ICS/LABA compared with ICS alone. Pedersen et al⁷³ provided further comment on the efficacy of combination ICS/LABA in reducing severe asthma exacerbations and reviewed evidence supporting the safety of LABAs, especially when combined with an ICS in a single delivery device. Szeffler and Busse⁷⁴ provided a recent commentary on the LABA controversy in view of ongoing concerns regarding the issue of stepping down on LABA or ICS therapy when control is established with the ICS/LABA combination.

On the basis of several prior studies, it has been shown that anti-IgE therapy has the potential to reduce severe asthma exacerbations; however, there are lingering concerns over the adverse effects of this medication, including the risk for malignancy. Busse et al⁷⁵ provided reassuring information based on a pooled analysis of available data from clinical trials on omalizumab-treated patients, including children, adolescents, and adults, that an increased risk of malignancy is unlikely. Other biologic response or immunomodulator therapies are being developed, including an anti-IL-4 receptor α antagonist. Slager et al⁷⁶ reported on a significant pharmacogenetic interaction between anti-IL-4 α therapy and *IL4A* gene variation associated with a better response to therapy in reducing asthma exacerbations.

Improving symptom control in children with asthma

Meltzer et al⁷⁷ reported on asthma burden in the United States from the 2009 Asthma Insight and Management Survey and indicated that it remains high despite the availability of updated

treatment guidelines and new therapies. Kit et al⁷⁸ reported that preventive asthma medication use among children is increasing among children and adolescents, but racial and ethnic disparities, including those who are uninsured, exist in the use of these medications.

Despite reported efficacy of long-term controllers in children with asthma, there are concerns regarding the adverse effects of these medications, including the effect of ICSs on growth.⁷⁹ This has prompted alternative strategies for stepping down therapy and limiting exposure to ICSs. One strategy is to use ICSs on an intermittent basis when symptoms occur. However, we must be sure that sufficient studies are in place to justify this form of treatment and that parents and patients are not confused by using intermittent ICS treatment when continuous is actually needed.⁸⁰

Shi et al⁸¹ reported that impulse oscillometry in children could be useful in assessing asthma control, as reflected by small airways dysfunction. However, there is limited information on baseline values in healthy children for this measure, and thus additional data are necessary before cut points can be used.

An alternative to ICS therapy is leukotriene receptor antagonist therapy, such as montelukast. Questions have been raised regarding the adverse effects of this medication. Schumock et al⁸² reported that use of these medications is not associated with an increased risk of suicidal attempts in children and adolescents, but there was a trend for increased risk in those 19 to 24 years of age that merits further evaluation. Ingelsson et al⁸³ evaluated incident and recurrent cardiovascular disease associated with montelukast use. They provided a first indication of a potential role of this medication for secondary prevention of cardiovascular disease. Duong et al⁸⁴ reported that montelukast, or a medium-dose ICS, alone or in combination, provided comparable and modest attenuation of severe exercise-induced bronchospasm in asthma management. Combination therapy offered an added benefit of a shorter duration and time to recovery from exercise-induced bronchospasm and a higher rate of response.

Oh et al⁸⁵ reported that maternal smoking while *in utero* was associated with poor asthma control in black and Latino subjects assessed at age 8 to 17 years. These findings increase the importance of smoking prevention and cessation during pregnancy to improve asthma control and reduce health disparities.

There is a growing level of concern regarding the potential risk of acetaminophen in children with asthma. Kreiner-Moller et al⁸⁶ provided data to suggest that acetaminophen is associated with early childhood asthma; however, they pointed out that further studies are needed to confirm an independent association. Stephenson et al⁸⁷ provide preliminary observations suggesting that acetaminophen detoxification might be impaired in symptomatic children with moderate-to-severe asthma as a function of altered glutathione homeostasis. However, more information is needed on mechanistic and clinical studies to understand acetaminophen-asthma associations. A study comparing acetaminophen and ibuprofen for pain and fever management in young children with early asthma is now in progress in the National Heart, Lung, and Blood Institute's AsthmaNet.

New information on severe asthma

Shikotra et al⁸⁸ provided information to show that thymic stromal lymphopoietin (TSLP) expression is increased in a subset of patients with severe asthma in spite of high-dose inhaled or oral steroid therapy. Because this cytokine might be responsible for

T_H2 -driven airway changes in murine animal models, anti-TSLP therapy could be effective in reducing TSLP expression and T_H2 inflammation. Tsitsiou et al⁸⁹ demonstrated that severe asthma is associated with the activation of circulating $CD8^+$ T cells but not $CD4^+$ T cells. Thus targeting $CD8^+$ cells might serve as another novel therapeutic approach. Brown et al⁹⁰ noted that children with severe asthma have increased airway TGF- β 1 expression and activation associated with an increased airway oxidant burden. Reducing TGF- β 1 activity could be another therapeutic target for improving asthma control by reducing the risk for airway remodeling. In addition, Bossley et al⁹¹ reported that severe therapy-resistant asthma in children is characterized by remodeling and variable airway eosinophil counts without neutrophilia. Of interest, the T_H2 mediators thought to drive allergic asthma were mostly absent. This suggests that new medications directed toward adult severe asthma, such as anti-IL-5, might not be effective in children, except for a subset.

Chippes et al⁹² reviewed key findings from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study, which included children, adults, and adolescents. As indicated in the report by Zeiger et al,⁶⁵ uncontrolled asthma is highly predictive of future asthma exacerbations. In addition, recent exacerbation history is the strongest predictor for future asthma exacerbations. Clinicians should be aware of the importance of good communication, a clear action plan, and monitoring adherence to prescribed treatment regimens.⁹² Ivanova et al⁹³ reported that adolescents and adults with moderate-to-severe persistent asthma who had exacerbations had higher total and asthma-related health care costs than those without exacerbations. Controller use was also higher in those with exacerbations, supporting the impetus to develop new medications for this group of patients. Jarjour et al⁹⁴ reported on lessons learned from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Future directions include recruitment of a larger number of subjects, including children, to allow for further characterization of anatomic, physiologic, biochemical, and genetic factors related to severe disease in a longitudinal assessment to identify factors that modulate the natural history of severe asthma and provide a mechanistic rationale for management strategies.

NEW INFORMATION ON RISK FACTORS FOR AND MANAGEMENT OF EARLY ASTHMA IN CHILDREN

The August 2012 theme issue was devoted to early asthma. The opening editorial, entitled "Early asthma: stepping closer to primary prevention," made the point that significant advances have been made in the overall management of asthma through better medications, guidelines for asthma, and new methods to measure outcomes through electronic medical records systems.⁹⁵ However, further advances must be made in the early diagnosis of asthma and in appropriate intervention that could potentially alter the course of the disease by preventing onset, persistence, and progression.

Mechanisms

Boyce et al⁹⁶ provided a timely review on the mechanisms of asthma, allergy, and immunology. They indicated that 2011 was marked by rapid progress in identification of basic mechanisms of allergic disease and the translation of these mechanisms into human cell systems. Various cells involved in innate and adaptive

immunity have received attention for their role in host defense mechanisms. For example, Sevician et al⁹⁷ provided information suggesting that the relation of IFN- γ production at birth to wheeze is only evident for boys and was limited to the first 2 years of life. James et al⁹⁸ reviewed the relationship between infections and asthma, indicating it is not yet fully understood. Therefore more information is needed to characterize the response in patients with asthma and atopic disease to improve control of these diseases, develop treatment strategies for those pathogens for which there are currently no therapies, and perhaps lead to prevention of disease development.

Manthei et al⁹⁹ reported that the purinergic receptor P2X₇ function is associated with asthma risk or disease severity, and the relationships appear to be age dependent. This receptor is associated with enhanced leukocyte recruitment to the airways. They propose that low P2X₇ function might decrease susceptibility to diseases, including asthma, and its functional capacity can be easily assessed in children.

Dendritic cells are known to play a central role in sensing the presence of foreign antigens and infectious agents and in initiating an appropriate immune response.¹⁰⁰ This cell could be a target for therapeutic intervention by influencing epithelial cell and dendritic cell interaction or by blocking IgE receptors on dendritic cells and might alter antiviral response.¹⁰⁰ As such, the epithelial cell plays a key role in the development and progression of asthma, and interventions to preserve its integrity could influence the course of asthma.¹⁰¹

A report from the Mechanism of the Development of Allergy Symposium by Anto et al¹⁰² defined phenotypes of allergic disease, including their relationship to asthma. They concluded that the factors that affect the course of development of allergy, the period in life in which they are triggered, and allergy mechanisms remain to be elucidated.

Durrani et al¹⁰³ reported that allergic asthmatic children have impaired innate immune responses to human rhinovirus (HRV) that correlate with increased high-affinity IgE receptor (Fc ϵ RI) expression on plasmacytoid dendritic cells and are reduced by Fc ϵ RI cross-linking. They proposed that these effects likely increase susceptibility to HRV-induced wheezing and asthma exacerbations. Chawes et al¹⁰⁴ studied bronchial responsiveness and lung function in 1-month-old neonates and concluded that bronchial hyperresponsiveness in at-risk neonates precedes acute bronchiolitis in response to infection with respiratory tract virus. This finding suggests a pre-existing common propensity to asthma and for the airways to react adversely to common respiratory tract viruses.

Genetics

Another predisposing feature of asthma could be related to genetic markers. Forno et al¹⁰⁵ evaluated genetic variants associated with early onset of childhood asthma. They identified 2 SNPs associated with earlier age of onset of childhood asthma in a combined analysis of 4 independent cohorts. Also, having at least 1 risk allele in any of the 2 earlier-onset SNPs is associated with lower lung function and higher medication use in childhood.

Spycher et al¹⁰⁶ reported that the genetic origins of asthma are diverse, and some pathways are specific to wheezing syndromes, whereas others are shared with atopy and bronchial hyperresponsiveness. They also provided information on etiologic differences among wheezing syndromes. Verlaan et al¹⁰⁷ confirmed the

association of rs4950928 with the allelic expression of *CH13LI* and the presence of a second functional SNP rs10399931, suggesting that these 2 SNPs are equally likely to modulate chitinase-3-like-1 gene (*CH13LI*) expression and susceptibility to asthma.

Torgerson et al¹⁰⁸ proposed that case-control admixture mapping is a promising strategy for identifying novel asthma-associated gene loci in Latino populations and implicated genetic variation at the 6q15 and 8q12 regions with asthma susceptibility. Torgerson et al¹⁰⁹ identified a novel asthma-associated locus on 6q and an SNP on 6q14.1 that is relevant to admixed populations with African ancestry and highlighted the importance of considering local ancestry in genetic association studies of admixed populations. Myers et al¹¹⁰ emphasized this point in reporting on 2 new gene loci associated with asthma that were identified in a European American population but not replicated in an African American and Latino population. On the other hand, Rumpel et al¹¹¹ noted a significant and independent association between genetic ancestry and severe asthma exacerbations among African American subjects with asthma, further emphasizing the role of admixture mapping in genetic analysis.

EARLY-LIFE EXPOSURES

Infection

Alcantara-Neves et al¹¹² provided support that the hygiene hypothesis is operating in an urban Latin American context but that its expression is restricted to the atopic status of patients and not the perceived asthma symptoms. They indicated that multiple pathogen exposures lead to more robust immune regulation and less atopy. Loss et al¹¹³ provided information regarding prenatal and early-life exposures and allergic outcomes. They indicated that farming-related exposures, such as raw milk consumption, that were previously reported to decrease the risk of allergic outcomes were associated with a change in gene expression of innate immunity receptors in early life.

Carroll et al¹¹⁴ reported that clinically significant rhinovirus infection during infancy was more strongly associated with having a mother with atopic asthma than clinically significant respiratory syncytial virus (RSV) infection. Also, infants with rhinovirus having a mother with atopic asthma was associated with increased risk of more severe illness. Sumino et al¹¹⁵ indicated that individual variations in the innate immune response to respiratory tract viruses are detectable even at birth, and these differences predict the susceptibility to acute respiratory tract illness during the first year of life. They suggest that a full analysis of interferon production pathways might provide key insights into the susceptibility of viral respiratory tract infections and subsequent chronic obstructive lung diseases, such as asthma.

Sykes et al¹¹⁶ provided data to show that rhinovirus induction of type I interferons in bronchoalveolar lavage cells is delayed and deficient and might be a marker of more severe asthma, as indicated by greater airway hyperresponsiveness and allergy. Baraldo et al¹¹⁷ reported that deficient interferon responses to rhinovirus infection are present in childhood in asthmatic subjects irrespective of their atopic status and in atopic patients without asthma. Jackson et al¹¹⁸ demonstrated, in a prospective repeated characterization of a birth cohort, that allergic sensitization precedes HRV wheezing and that the converse is not true. They suggested that therapeutics aimed at preventing allergic sensitization might modify virus-induced wheezing and the development of

asthma. In addition, Daley et al¹¹⁹ identified novel susceptibility genes for asthma and related traits and interactions between these genes and early-life viral infections.

Bacharier et al¹²⁰ reported that approximately 50% of children who experience severe RSV-induced bronchiolitis have a subsequent asthma diagnosis. They also noted that the presence of increased CCL5 (previously known as RANTES) levels in nasal epithelia at the time of bronchiolitis or the development of allergic sensitization by age 3 years are associated with increased likelihood of subsequent asthma. Adamko and Friesen¹²¹ commented on this study and indicated that hospitalization for RSV should warrant an overall reconsideration of the previous health status of a child and that underlying predisposition to chronic airway diseases in general should be sought even beyond asthma. A recent report by Krishnamoorthy et al¹²² provided information from animal studies suggesting that early infection with RSV impairs Treg cell function and increases susceptibility to allergic asthma by altering the lung microenvironment.

Akdis et al¹²³ discussed the roles of T_H17 and T_H22 cells in host defense and inflammatory diseases. IL-17 induces an inflammatory tissue response and is involved in the pathogenesis of several autoimmune diseases, whereas IL-22 plays a role in tissue protection and regeneration. Bachert et al¹²⁴ studied IgE to *Staphylococcus aureus* enterotoxins in adults and concluded that the IgE antibodies, but not IgE against inhalant allergens, are risk factors for asthma severity. They proposed that staphylococcal superantigens might be involved in the pathophysiology of severe asthma. Therefore the sum of the previous studies indicates the evolving role of bacterial and viral infection and asthma.

Environment

Heederik and von Mutius¹²⁵ reviewed the recent literature on microbial exposures and protective effects for asthma and allergy and the methodological issues that must be addressed. Illi et al¹²⁶ reported that a specific type of farm typical of traditional farming was protective against asthma, hay fever, and atopy. They indicated that specific farm characteristics were protective against asthma, but a link between hay fever and atopy remains to be identified, indicating different underlying protective mechanisms. Soto-Quiros et al¹²⁷ reported that high titers of IgE antibody to dust mite allergen were common and significantly increased the risk for acute wheezing provoked by rhinovirus among asthmatic children.

Reponen et al¹²⁸ reported information based on a birth cohort to indicate that exposure during pregnancy to 3 mold species common to water-damaged buildings was associated with childhood asthma at age 7 years. Rabinovitch¹²⁹ commented that this study and others highlight the importance of the environment and, more specifically, indoor air quality on asthma development and indicate that public policy interventions to reduce the effects of high indoor exposures, including those due to water damage, could reverse the upward trend in asthma prevalence over time.

Early presentation: phenotypes

Just et al¹³⁰ identified different phenotypes of recurrent wheezing in children by using cluster analysis. They noted that boys more frequently had atopic multiple-trigger wheezing with allergic environments, whereas girls had nonatopic uncontrolled wheezing associated with infectious agents. Wahn and Matricardi¹³¹ commented that the cross-sectional nature of the study

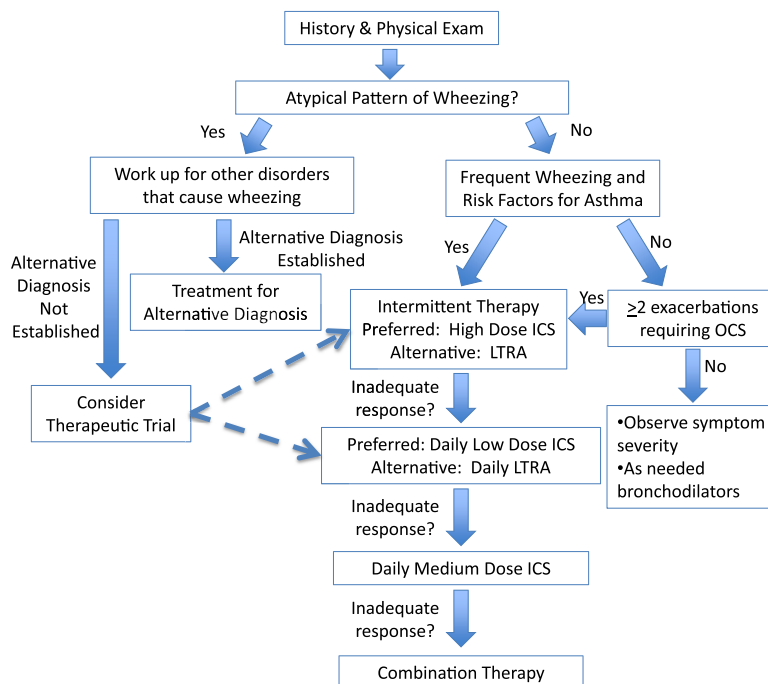


FIG 1. Proposed algorithm for the diagnosis and management of early childhood asthma. *LTRA*, Leukotriene receptor antagonist; *OCS*, oral corticosteroids. Used with permission from Bacharier and Guilbert.¹⁴⁰

does not allow one to answer whether these patterns related to sex are stable or change over time.

Herr et al¹³² indicated that atopy should be taken into consideration when assessing the risk of severe exacerbations in wheezing infants. They also recommended that infants with atopy should be protected against respiratory irritants, molds, and becoming overweight. Skytt et al¹³³ reported that a quantitative global assessment of significant troublesome symptoms in the first 3 years of life is a better predictor of asthma than assessment of wheeze. They also suggested that relying on the symptom of wheeze will lead to undertreatment. In a follow-up communication, Bisgaard et al¹³⁴ stated that the conceptual understanding of wheeze is inconsistent, and reliance on parental report of wheeze might lead to delays in seeking medical care, undertreatment of asthma attacks, and inaccurate research classifications. Matsui¹³⁵ commented on these 2 reports as recommending a broader view of respiratory symptoms rather than focusing on wheeze alone. The studies underscore the importance of educating parents of asthmatic patients about nonwheezing respiratory symptoms and their importance as indicators of asthma control and an imminent exacerbation.

Grad and Morgan¹³⁶ reviewed longitudinal cohorts that indicate wheezing that begins in early life and continues into the school years generally persists into childhood. They noted that allergic sensitization early in life, early-life infection with rhinovirus, or colonization with any number of bacteria has been associated with increased risk of persistent wheeze. Also, deficits in lung function in childhood can persist into adulthood and perhaps put subjects at risk for the later development of chronic obstructive pulmonary disease. Savinije et al¹³⁷ reviewed the use of clinical prediction rules in assessing children who will have asthma at school age among preschool children. They concluded that prediction can be improved by more precise definitions and measures and, ultimately, by more knowledge on pathophysiologic mechanisms.

Bisgaard et al¹³⁸ reported that children with asthma by age 7 years have lung function deficits and increased bronchial responsiveness as neonates. Furthermore, they indicated that the lung deficit seems to progress to age 7 years. Therefore research into the origins of asthma should consider early life before and after birth. Smyth¹³⁹ reviewed the lessons and limitations of birth cohorts in childhood asthma and concluded that epidemiologic research in young children with wheezing has proved difficult to apply in clinical practice. There is a need to develop more precise definitions to identify mechanisms that might lead to novel therapeutic interventions to prevent allergic sensitization and asthma.

Management

Bacharier and Guilbert¹⁴⁰ reviewed the diagnosis and management of early asthma in children. They indicated that early childhood wheezing and asthma are heterogeneous disorders with many phenotypic and variable expressions during childhood, and they provided a systematic approach to evaluation and intervention (Fig 1).¹⁴⁰ However, this approach is based largely on expert opinion and extrapolation from studies in older children because high-quality trials are few in this important age group. Prevention might require the use of biologic response modifiers during a window of opportunity to prevent emergence, progression, or both of the disease. Ballou et al¹⁴¹ reviewed the available immune response modifiers for asthma and concluded that novel therapies must be directed at specific asthma endotypes if these new treatment modalities are going to be clinically efficacious and moved from the point of research investigation to clinical application. Perhaps asthma defined by molecular biology, including epigenetic markers, will lead to new approaches in management similar to those now being considered in cancer therapy.¹⁴²

SUMMARY

Reports in the *Journal* over the past year have contributed new information on the benefits of systems management, indicators of disease activity, the role of allergy and infection in the development of asthma, and greater attention to evaluating and managing early asthma in children. The next steps include using this information to help identify young children at risk for asthma, applying early intervention with available therapies, and conducting further studies to identify more effective strategies to alter the course of the disease.

Key advances in pediatric asthma in 2012

- Periostin is a systemic biomarker of airway eosinophilia in asthmatic patients and has the potential utility in patient selection for emerging asthma therapies targeting T_H2 inflammation.²⁰
- Epigenetic mechanisms provide a promising line of inquiry that might, in part, explain the inheritance and immunobiology of asthma.²³
- Vitamin D supplementation might enhance corticosteroid responsiveness and control atopy and thereby improve asthma control in children.³⁹
- Airway epithelial cells from children with mild asthma exhibit greater expression of factors, including TGF- β , vascular endothelial growth factor, and periostin, associated with subepithelial airway remodeling than cells from atopic and healthy children.⁴⁴
- The National Institutes of Health (NIH) Asthma Outcomes Task Force provided a report on the definition of asthma outcomes that should be used in conducting NIH research.⁵⁰⁻⁵⁸
- Lung function can be used to predict hospitalizations, emergency department visits, and need for oral corticosteroid therapy in pediatric patients.⁶⁶
- A significant pharmacogenetic interaction between anti-IL-4 α therapy and *IL4A* gene variation is associated with a better response to therapy in reducing asthma exacerbations.⁷⁶
- Dendritic cells could be a target for therapeutic intervention by influencing epithelial cell and dendritic cell interaction or blocking IgE receptor on dendritic cells and might alter antiviral response.¹⁰⁰
- Deficient interferon responses to rhinovirus infection are present in childhood in asthmatic patients irrespective of their atopic status and in atopic patients without asthma.¹¹⁷
- Deficits in lung function in childhood can persist into adulthood and perhaps put subjects at risk for the later development of chronic obstructive pulmonary disease.¹³⁶

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