



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

 Current Opinion in
Immunology

New insights into asthma pathogenesis and treatment

 Stanley J Szeffler¹ and Azzeddine Dakhama²

Although national asthma guidelines help organize standards for asthma care, current asthma management is still primarily symptom based. Recent reports provide insights on how to improve asthma management through steps to better understand the natural history of asthma, individualize asthma care, reduce asthma exacerbations, manage inner city asthma, and some potential new ways to use available medications to improve asthma control. Despite many significant gains in managing asthma, we must now find improved strategies to prevent asthma exacerbations, alter the natural history of the disease, and to reduce health disparities in asthma care. Perhaps new directions in personalized medicine including a systems biology approach, along with improved health care access and communication will lead to better methods to alleviate the burden of asthma. This review will discuss the benefits and limitations of the current approach to asthma management, new studies that could impact new directions in asthma management, and new insights related to mechanisms of asthma and allergic airways inflammation that could eventually lead to improved asthma control.

Addresses

¹ Helen Wohlberg & Herman Lambert Chair in Pharmacokinetics, Divisions of Pediatric Clinical Pharmacology and Allergy and Immunology, Department of Pediatrics, National Jewish Health, University of Colorado School of Medicine, Denver, CO 80206, USA

² Department of Pediatrics, National Jewish Health, University of Colorado School of Medicine, Denver, CO 80206, USA

Corresponding author: Szeffler, Stanley J (szefflers@njhealth.org)

Current Opinion in Immunology 2011, **23**:1–7

This review comes from a themed issue on
 Allergy and hypersensitivity
 Edited by Bart Lambrecht and Donald Leung

0952-7915/\$ – see front matter
 © 2011 Elsevier Ltd. All rights reserved.

DOI [10.1016/j.coi.2011.07.014](https://doi.org/10.1016/j.coi.2011.07.014)

Introduction

Asthma affects approximately 25 million people in the United States including 7 million children. This review will highlight asthma management principles and present new information that impacts our understanding of asthma and a personalized approach to asthma care. Collaboration of researchers, clinicians, patients, health care providers, and federal agencies should advance asthma care.

Current status of asthma management

The approach to management is directed at asthma control [1^{••},2,3]. While clinicians use a patient-centered approach to select a medication, dose and delivery system, they do not currently utilize patient characteristics, biomarkers, and genetics to select and adjust treatment. Targets have been set to reduce hospitalizations and urgent care utilization by developing a systemic approach to managing asthma. New tools to monitor disease activity, including biomarkers and epigenetic markers, hold promise for identifying gaps in disease management and should prompt the development of immunomodulator therapy [4]. Considerable work remains to be done to reduce the burden of disease [1^{••}].

New insights from recent clinical studies

In young children with recurrent wheeze, the benefits of asthma therapies need to be balanced with assessment of risk [5]. A translational research approach based on longitudinal symptom patterns combined with a systems biology approach may prove useful [6]. Prenatal factors might predispose an infant to develop asthma. Maternal contact with different farm animal species and barns and consumption of farm-produced butter during pregnancy can enhance the production of pro-inflammatory cord blood cytokines, whereas maternal consumption of farm-produced yogurt results in significantly lower levels of interferon-gamma and interferon-alpha in umbilical blood [7].

Controversy continues to rage over the role of acetaminophen on either causing or exacerbating asthma in children. However, confounding factors are difficult to control in observational studies related to acetaminophen because the allocation to treatment groups does not take place randomly [8,9].

Genetic testing is not ready for application to predict the natural history of asthma [10]. CD14 is a pattern-recognition receptor for environmental lipopolysaccharide. CD14 methylation increases significantly from age 2 to 10 years, and the level of methylation is inversely correlated with sCD14 levels at 10 years of age [11]. This age-related change could play a role in differential influence of gene polymorphisms on gene transcription and subsequent disease.

Infection plays a significant role in asthma morbidity. Most studies have focused on viral infections including rhinovirus [12,13]. Interest in other microbiota has also been enhanced by new techniques to measure bacteria composition. The composition of bronchial airway

2 Allergy and hypersensitivity

microbiota is associated with bronchial hyperresponsiveness among patients with suboptimally controlled asthma [14].

Information continues to evolve regarding the role of the environment in the development of asthma (Figure 1). Certain genes are involved in the development and function of regulatory T cells, specifically IL2RA, TLR2, TGFBR2, and FOXP3, and are associated with atopy and asthma by gene–gene interaction [15]. Modeling of multiple gene–gene interactions should unravel genetic susceptibility to atopy and asthma. In addition, children living on farms are exposed to a wider range of microbes and this exposure explains a substantial fraction of the protective effect on asthma [16•]. Common genetic polymorphisms are unlikely to moderate the protective influence of the farming environment but rare variants may do so [17]. Based on research findings related to microbiota in the gut, interventional approaches might create a healthy microbiota that confers maximum tolerogenic immunomodulatory effects [18].

The Asthma Predictive Index (API) is a useful clinical checklist to identify children at risk for asthma [19]. Remitting, periodic, and persistent asthma in adolescence was recently reported from a long-term study of childhood asthma [20•]. Remission is infrequent and not affected by previous anti-inflammatory controller therapy.

On the road to personalized medicine

The Commissioner of the Food and Drug Administration and the Director of the National Institutes of Health have focused attention on personalized medicine [21]. Key studies from two NHLBI asthma networks identified variable response to several long-term controller therapies, specifically inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) [22]. Patient characteristics including age and allergic status and biomarkers are associated with response to ICS and LTRA.

Exhaled nitric oxide, a biomarker of allergic airway inflammation, can now be easily obtained. Multiple-trigger wheezers are more likely to have abnormal pulmonary function and increased fraction of exhaled nitric oxide (FeNO) than episodic (viral) wheezers [23]. High FeNO identifies those patients with severe asthma characterized by the greatest airflow obstruction and hyperinflation and most frequent use of emergency care [24]. In addition, high urinary LTE₄/FeNO ratios are associated with a better response to montelukast than fluticasone propionate in children with mild-to-moderate asthma [25].

A recent study evaluated step-up therapy in school-age children with asthma uncontrolled on low-dose ICS [26•]. Nearly all children demonstrated differential responses, with best response more than one-and-a-half times as

likely with long-acting β -adrenergic agonist (LABA) step-up. However, many children demonstrated their best response to ICS or LTRA step-up. The biomarkers and genetics evaluated in this study were not helpful in selecting the participants most probably to respond to one of the three treatment choices.

Developing a systematic approach for studying disorders such as asthma will depend on well-characterized cohorts with in-depth phenotyping, including lung imaging, and assessment of gene expression to introduce systems biology-based management [27]. Additional tools such as epigenetics will define the interplay between genetic and environmental factors that result in disease progression [28•]. Severe asthma in children is characterized by a distinct airway molecular phenotype that does not have a clear TH1 or TH2 pattern [29,30]. Identification of genes associated with loss of lung function in this population, such as hedgehog interacting protein on chromosome 4q31, will be important to verify [31].

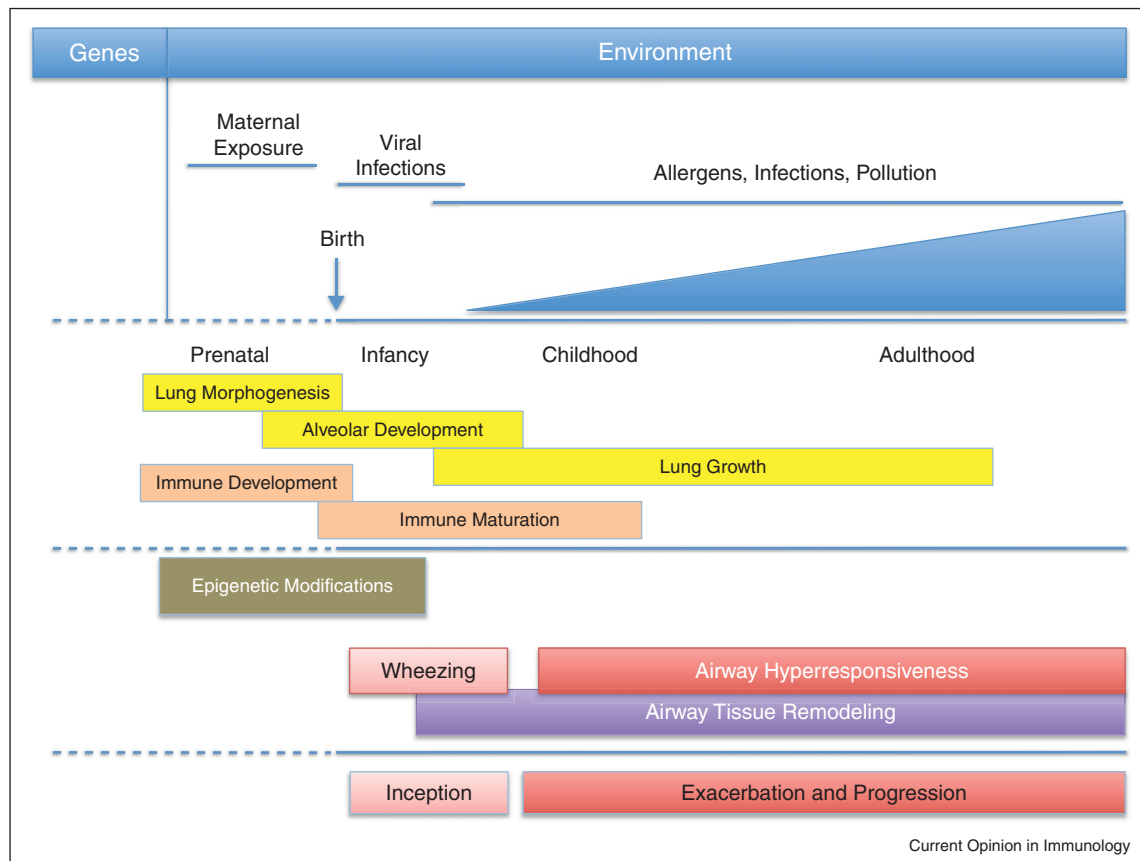
Respiratory infection is the most common cause of acute asthma exacerbations [32]. The primary risk factor for atopic asthma is sensitization to perennial aeroallergens resulting from a failure to generate protective immunologic tolerance [33]. Perturbation of the balance between innate and adaptive immune pathways is believed to be the basis for disease expression, and in the specific case of atopic asthma, the prototypic example of this is acute exacerbations triggered by viral infections.

Human rhinovirus infections are nearly universal in children with asthma during common cold seasons. Illnesses associated with viruses have greater duration and severity and atopic asthmatic children experience more frequent and severe virus-induced illnesses. Bronchial epithelial cells from asthmatics are more susceptible to rhinovirus infection owing to deficient interferon- β production, and normal antiviral response can be restored in these cells with exogenous interferon- β [34]. A recent report noted that susceptibility to recurrent acute asthma exacerbations is associated with an O-secreter mucin glycan phenotype [35•].

Asthma exacerbations, especially in children, are associated with the fall season. Treatment with omalizumab, anti-IgE, significantly attenuates seasonal peaks in asthma exacerbations in inner-city children [36•]. Even at relatively low ambient concentrations, ozone and primary pollutants from traffic sources independently contribute to the burden of emergency department visits for pediatric asthma [37].

Asthma in inner-city children is prevalent, has increased severity, and is often difficult to control. A key goal is to define mechanisms of immune system deviation and immune tolerance [38]. A systematic guidelines-based

Figure 1



Interacting Factors in Asthma Development and Persistence.

Asthma may originate early in life, determined by complex gene-environment interactions. The perinatal phase is a crucial window of susceptibility because the lung is still developing and the immune system lacks the ability to adequately respond to the environment. Infection of the lower respiratory tract with viruses during infancy trigger an inflammatory response that may persist longer with allergies and subsequently progress to clinical asthma in early childhood. Once established, asthma may persist and becomes heterogeneous with various environmental exposures. Interventions early in life may alter the natural history of asthma, and better control of symptoms, especially asthma exacerbations, may help prevent its progression into more severe forms of the disease.

approach improves asthma control significantly [39]. The future challenges for improving management of asthma in inner city children include further studies on defining the cause of asthma, assessing the role of specific allergens, and interrupting the interaction of viral infections with the atopic phenotype.

Opportunities to improve asthma control

Over the past 20 years we have seen a significant reduction in asthma mortality, the introduction of new medications, and less steroid-requiring asthma, especially in children [1^{••}]. Now we must look at methods to improve overall asthma control. Tiotropium bromide, a long-acting anticholinergic therapy, was evaluated in a crossover trial in adult asthma patients inadequately controlled on low dose ICS [40]. It improved symptoms and lung function and its effects appeared to be equivalent to salmeterol and exceeded higher dose ICS therapy.

Dietary insufficiency, including vitamin D, has a potential relationship to childhood asthma. Low serum 25-hydroxyvitamin D levels have been associated with increased risk for rhinovirus, respiratory syncytial virus and virus co-infections [41]. Vitamin D insufficiency is common in North American children with mild-to-moderate persistent asthma and is associated with higher odds of severe exacerbations [42]. Corticosteroid use and worsening airflow limitation is associated with lower vitamin D serum levels in asthmatic patients [43]. Vitamin D enhances glucocorticoid action in PBMCs from asthmatic patients and also enhances the immunosuppressive function of dexamethasone. Prospective studies along with carefully developed mechanistic components are needed to validate the benefits of vitamin D in asthma management.

A novel nutritional formula (NNF) enriched in eicosa-pentaenoic (EPA) and gamma-linolenic fatty acids and

4 Allergy and hypersensitivity

antioxidants was evaluated in asthmatic children [44]. The NNF-treated group had reduced biomarkers of disease activity and studies are needed to evaluate the role of NNF in improving asthma control. Another recent direction has been to reduce the requirement for daily long-term controller therapy. In those children who are well controlled on low-dose ICS therapy, a reasonable step-down approach is to combine intermittent ICS use with rescue bronchodilator use as needed. This strategy is more effective than stepping down to rescue bronchodilator use alone in preventing asthma exacerbations [45•].

New insights into biologic mechanisms

Asthma is increasingly recognized as a heterogeneous disease with respect to clinical phenotypes, immunopathology and response to therapy, which calls for better understanding of the disease and improved therapies [46]. Clinically, based on the presence or absence of IgE to common allergens, asthma may be divided into allergic and non-allergic subtypes, which share many similarities providing evidence against classification under distinct immunopathological entities [47].

While allergens are known to play a significant role in driving allergic airway inflammation, little is known about non-allergic asthma. Asthma is considered a Th-2 cell-mediated airways inflammatory disorder with tissue eosinophilia, remodeling and altered airway function. Other T cell phenotypes including Th-17, iNK-T cells, and nuocytes (non-T non-B helper T cells) also contribute to the pathogenesis of asthma [48••].

The hallmark feature of asthma is airway hyperresponsiveness (AHR), defined by excessive airway narrowing, usually reversed with bronchodilators that relax airway smooth muscle (ASM). It is not clear if this altered response is due to abnormal smooth muscle or to a normal smooth muscle operating in an abnormal airway tissue environment [49••]. Nonetheless, there is a general agreement that the total amount of smooth muscle is increased in the airways of asthmatics, which may lead to increased force-generating contraction, and early computational models predicted that thickening of ASM is the primary cause of excessive narrowing seen in the asthmatic airway [50].

Asthma is characterized by airway wall remodeling, which appears to correlate with severity but not duration [51••]. However, not all aspects of airway remodeling are deleterious [52]. For example, the stiffening of airway wall that occurs in asthma as a result of increased extracellular matrix deposition could limit airway narrowing and excessive mucosal folding. Other aspects of remodeling such as airway wall thickening with edema have little effect on airway narrowing [53]. Bronchoconstriction, in the absence of inflammation could induce airway remodeling, suggesting that repeated stress on the airway could have a long-term effect [54•].

The origin of asthma can be traced to early onset wheezing during the first 3 years of life, most commonly triggered by repeated viral lower respiratory tract infections [55–58]. Thickening of the RBM can occur at 1–3 years of age in children with documented wheezing [59•]. Airway remodeling can develop independent of atopy in preschool children with multi-trigger wheezing [60]. Whether viral infections are truly the cause or simply a marker of the disease remains to be determined [13,61].

Asthma can develop in the absence of atopy and only a minority of allergic subjects develops asthma. Similarly, viral respiratory tract infections occur frequently but not all children will develop asthma, suggesting that common host susceptibility determines asthma independent of atopy. Perhaps an altered airway innate immune response could be a link connecting early life viral infection and subsequent development of persistent asthma [62]. If so, interventions aimed at minimizing the impact of early viral infections may alter the natural course of asthma in susceptible children.

Disclosure

Dr. Szefer has received fees from Boehringer-Ingelheim, Genentech, Glaxo Smith Kline, Merck, and Novartis for participating in respiratory advisory panels and from Merck in support of a lecture. Within the past three years, he received research support from Glaxo Smith Kline for a health outcomes study. Dr. Dakhama has no conflict of interest.

Acknowledgements

Drs. Szefer and Dakhama would like to thank Gretchen Hugen for assistance with this manuscript preparation. Dr. Szefer is supported by Public Health Services Research Grants HR-16048, HL64288, HL 51834, AI-25496, HL081335, HL075416, P01 ES018181 and the Colorado Cancer, Cardiovascular and Pulmonary Disease Program. Supported partly by Colorado CTSA grant 1 UL1 RR025780 from the National Institutes of Health (NIH) and National Center for Research Resources (NCRR). Dr. Dakhama is supported by NIH grants R01HD053557 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and P01ES018181 from the National Institute of Environmental Health Sciences.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Szefer SJ: **Advancing asthma care: the glass is only half full!!** *J Allergy Clin Immunol* 2011, in press, PMID: 21722795. This is a current review of the accomplishments to date from the past 30 years regarding asthma care in the United States. It also reviews steps to be taken in the next 10 years to reduce the burden of this disease. It is an introduction to a series of articles reviewing various aspects of asthma research.
2. Szefer SJ: **Advances in pediatric asthma in 2010: addressing the major issues.** *J Allergy Clin Immunol* 2011, **127**:102-115.
3. Apter AJ: **Advances in adult asthma diagnosis and treatment and HEDQ in 2010.** *J Allergy Clin Immunol* 2011, **127**:116-122.

4. Holgate ST: **Pathophysiology of asthma: what has our current understanding taught us about new therapeutic approaches?** *J Allergy Clin Immunol* 2011, in press, PMID: 21807404.
5. Guilbert T: **Identifying and managing the infant and toddler at risk for asthma.** *J Allergy Clin Immunol* 2010, **126**:417-422.
6. Bisgaard H, Bennelykke K: **Long-term studies of the natural history of asthma in childhood.** *J Allergy Clin Immunol* 2010, **126**:187-197.
7. Pfeferle PI, Buchele G, Blumer N, Roponen M, Ege MJ, Krauss-Etschmann S, Genuneit J, Hyvarinen A, Hirvonen MR, Lauener R *et al.*: **Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy: the PASTURE Study.** *J Allergy Clin Immunol* 2010, **125**:108-115.
8. Tapiainen T, Dunder T, Mottonen M, Pokka T, Uhari M: **Adolescents with asthma or atopic eczema have more febrile days in early childhood: a possible explanation for the connection between paracetamol and asthma?** *J Allergy Clin Immunol* 2010, **125**:751-752.
9. Schnabel E, Heinrich J, the LISA Study Group: **Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood.** *J Allergy Clin Immunol* 2010, **126**:1071-1073.
10. Holloway JW, Arshad SH, Holgate ST: **Using genetics to predict the natural history of asthma?** *J Allergy Clin Immunol* 2010, **126**:200-209.
11. Munthe-Kaas MC, Maehre Torjussen T, Gervin K, Ledrup Carlsen KC, Hakon Carlsen K, Granum B, Hjorthaug HS, Undlien D, Lyle R: **CD14 polymorphisms and serum CD14 levels through childhood: a role for gene methylation?** *J Allergy Clin Immunol* 2010, **125**:1361-1368.
12. Rosenthal LA, Avila PC, Heymann PW, Martin RJ, Miller EK, Papadopoulos NG, Peebles RS, Gern JE, Infections and Asthma Committee Environmental and Occupational Respiratory Diseases Interest Section, American Academy of Allergy, Asthma & Immunology: **Viral respiratory tract infections and asthma: the course ahead.** *J Allergy Clin Immunol* 2010, **125**:1212-1217.
13. Sly PD, Kusel M, Holt PG: **Do early-life viral infections cause asthma?** *J Allergy Clin Immunol* 2010, **125**:1202-1205.
14. Huang YJ, Nelson CE, Brodie EL, DeSantis TZ, Baek MS, Liu J, Woke T, Allgaier M, Bristow J, Wiener-Kronish JP *et al.*: **Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma.** *J Allergy Clin Immunol* 2011, **127**:372-381.
15. Bottema RWB, Kerkhof M, Reijmerink NE, Thijs C, Smit HA, van Schayck CP, Brunekreef B, van Oosterhout AJ, Postma DS, Koppelman GH: **Gene-gene interaction in regulatory T-cell function in atopy and asthma development in childhood.** *J Allergy Clin Immunol* 2010, **126**:338-346.
16. Ege MJ, Mayer M, Normand A-C, Genuneit J, Cookson WOCM, Braun-Fahrlander C, Heederik D, Piarroux R, von Mutius E: **Exposure to environmental microorganisms and childhood asthma.** *N Engl J Med* 2011, **364**:701-709.
This is an important study that evaluated the exposures to environmental microorganisms in relation to the development of childhood asthma. The investigators noted that children living on farms were exposed to a wider range of microbes than a reference group. They concluded that this exposure explains a substantial fraction of the inverse relation between asthma and growing up on a farm.
17. Ege MJ, Strachan DP, Cookson WOCM, Moffatt MF, Gut I, Lahrop M, Kabesch M, Genuneit J, Buchele G, Sozanska B *et al.*: **Gene-environment interaction for childhood asthma and exposure to farming in Central Europe.** *J Allergy Clin Immunol* 2011, **127**:138-144.
18. McLoughlin RM, Mills KHG: **Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma.** *J Allergy Clin Immunol* 2011, **127**:1097-1107.
19. Castro-Rodriguez JA: **The Asthma Predictive Index: a very useful tool for predicting asthma in young children.** *J Allergy Clin Immunol* 2010, **126**:212-216.
20. Covar RA, Strunk R, Zeiger RS, Wilson LA, Liu AH, Weiss S, Tonascia J, Spahn JD, Szeffler SJ, for the Childhood Asthma Management Program Research Group: **Predictors of remitting, periodic, and persistent childhood asthma.** *J Allergy Clin Immunol* 2010, **125**:359-366.
This study evaluated long-term outcomes of children enrolled in the NHLBI Childhood Asthma Management Program following an initial 5–6 year randomized trial that included two forms of anti-inflammatory therapy as compared to as needed bronchodilator therapy. Asthma was identified as remitting in 6%, periodic in 39%, and persistent in 55% of the 909 participants, with no effect noted from earlier anti-inflammatory treatment during this trial.
21. Hamburg MA, Collins FS: **The path to personalized medicine.** *N Engl J Med* 2010, **363**:301-304.
22. Szeffler SJ, Martin RJ: **Lessons learned from variation in response to therapy in clinical trials.** *J Allergy Clin Immunol* 2010, **125**:285-292.
23. Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, Aurora P: **Symptom-pattern phenotype and pulmonary function in preschool wheezers.** *J Allergy Clin Immunol* 2010, **126**:519-526.
24. Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SAA, Bleecker E, Busse W, Calhoun WJ, Castro M *et al.*: **Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma.** *Am J Respir Crit Care Med* 2010, **181**:1033-1041.
25. Rabinovitch N, Graber NJ, Chinchilli VM, Sorkness CA, Zeiger RS, Strunk RC, Bacharier LB, Martinez FD, Szeffler SJ, for the Childhood Asthma Research and Education Network of the National Heart Lung and Blood Institute: **Urinary leukotriene E4/exhaled nitric oxide ratio and montelukast response in childhood asthma.** *J Allergy Clin Immunol* 2010, **126**:545-551 [erratum: *J Allergy Clin Immunol* 2010;126:959–60].
26. Lemanske R, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, Strunk RC, Szeffler SJ, Zeiger RS, Bacharier LB, *et al.*: **for the Childhood Asthma Research and Education Network of the National Heart, Lung and Blood Institute: Step-up therapy for children with uncontrolled asthma while receiving inhaled corticosteroids.** *N Engl J Med* 2010, **362**:975-985.
This is a multicenter clinical trial conducted by the NHLBI Childhood Asthma Research and Education Network to evaluate three different strategies in stepping up asthma therapy in patients inadequately controlled on low-dose inhaled corticosteroids. An innovative approach to evaluate multiple asthma outcomes was introduced in this study to assess differential response to treatment.
27. Auffray C, Adcock IM, Chung KF, Djukanovic R, Pison C, Sterk PJ: **An integrative systems biology approach to understanding pulmonary diseases.** *Chest* 2010, **137**:1410-1416.
28. Yang IV, Schwartz DA: **Epigenetic control of gene expression in the lung.** *Am J Respir Crit Care Med* 2011, **183**:129-1301.
A review of epigenetics and the role it could play in understanding the dynamic biology of the lung and the potential development of novel diagnostic and therapeutic approaches to lung disease including asthma.
29. Fitzpatrick AM, Higgins M, Holguin F, Brown LAS, Teague WG, for the National Institutes of Health/National Heart, Lung and Blood Institute's Severe Asthma Research Program: **The molecular phenotype of severe asthma in children.** *J Allergy Clin Immunol* 2010, **125**:851-857.
30. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, Wenzel SE, Aujla S, Castro M, Bacharier LB *et al.*: **Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung and Blood Institute Severe Asthma Research Program.** *J Allergy Clin Immunol* 2011, **127**:382-389.
31. Li X, Howard TD, Moore WC, Ampleford EJ, Li H, Busse WW, Calhoun WJ, Castro M, Chung KF, Erzurum SC *et al.*: **Importance of hedgehog interacting protein and other lung function genes in asthma.** *J Allergy Clin Immunol* 2011, **127**:1457-1465.
32. Jackson DJ, Johnston SL: **The role of viruses in acute exacerbations of asthma.** *J Allergy Clin Immunol* 2010, **125**:1178-1187.

6 Allergy and hypersensitivity

33. Holt PG, Strickland DH: **Interactions between innate and adaptive immunity in asthma pathogenesis: new perspectives from studies on acute exacerbations.** *J Allergy Clin Immunol* 2010, **125**:963-972.
34. Cakebread JA, Xu Y, Grainge C, Kehagia V, Howarth PH, Holgate ST, Davies DE: **Exogenous IFN- β has antiviral and anti-inflammatory properties in primary bronchial epithelial cells from asthmatic subjects exposed to rhinovirus.** *J Allergy Clin Immunol* 2011, **127**:1148-1154.
35. Innes A, Wong McGrath K, Dougherty RH, McCulloch CE, Woodruff PG, Seibold MA, Okamoto KS, Ingmundson KJ, Solon MC, Carrington SD *et al.*: **The H antigen at epithelial surfaces is associated with susceptibility to asthma exacerbation.** *Am J Respir Crit Care Med* 2011, **183**:189-194.
This study shows how blood group antigen structures on mucin glycans influence susceptibility to asthma exacerbation and suggests that new approaches to prevent exacerbations could be developed.
36. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA *et al.*: **Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children.** *N Engl J Med* 2011, **364**:1005-1015.
This study evaluated the role of anti-IgE in improving asthma control in inner city children. When added to a regimen of guidelines-based therapy, omalizumab further improved asthma control, nearly eliminated seasonal peak exacerbations, and reduced the need for other medications to control asthma.
37. Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA, Sarnat SE, Mulholland JA, Tolbert PE: **Short-term associations between ambient air pollutants and pediatric asthma emergency department visits.** *Am J Respir Crit Care Med* 2010, **182**:307-316.
38. Togias A, Fenton MJ, Gergen PJ, Rotrosen D, Fauci AS: **Asthma in the inner city: the perspective of the National Institute of Allergy and Infectious Diseases.** *J Allergy Clin Immunol* 2010, **125**:540-544.
39. Szefer SJ, Gergen PJ, Mitchell H, Morgan W: **Achieving asthma control in the inner city: do the National Institutes of Health Asthma Guidelines really work?** *J Allergy Clin Immunol* 2010, **125**:521-526.
40. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes WT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, *et al.*: for the National Heart, Lung and Blood Institute's Asthma Clinical Research Network: **Tiotropium bromide step-up therapy for adults with uncontrolled asthma.** *N Engl J Med* 2010, **363**:1715-1726.
41. Jartti T, Ruuskanen O, Mansbach JM, Vuorinen T, Camargo CA: **Low serum 25-hydroxyvitamin D levels are associated with increased risk of viral co-infections in wheezing children.** *J Allergy Clin Immunol* 2010, **126**:1074-1076.
42. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, Weiss ST, Litonjua AA, for the Childhood Asthma Management Program Research Group: **Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study.** *J Allergy Clin Immunol* 2010, **126**:52-58.
43. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DYM: **Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use.** *J Allergy Clin Immunol* 2010, **125**:995-1000.
44. Covar R, Gleason M, Macomber B, Stewart L, Szefer SJ, Engelhardt K, Murphy J, Liu A, Wood S, DeMichele S *et al.*: **Impact of a novel nutritional formula on asthma control and biomarkers of allergic airway inflammation in children.** *Clin Exp Allergy* 2010, **40**:1163-1174.
45. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT, Strunk RC, Szefer SJ, Zeiger RS, Bacharier LB *et al.*: **Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomized, double-blind, placebo-controlled trial.** *Lancet* 2011, **377**:650-657.
This study evaluated a step-down approach in children who are adequately controlled on low-dose inhaled corticosteroids. A key finding was the benefits of as needed inhaled corticosteroid when combined with rescue bronchodilator as compared to stepping down to as needed rescue bronchodilator alone in preventing exacerbations.
46. Anderson GP: **Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease.** *Lancet* 2008, **372**:1107-1119.
47. Humbert M, Menz G, Ying S, Corrigan CJ, Robinson DS, Durham SR, Kay AB: **The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences.** *Immunol Today* 1999, **20**:528-533.
48. Lloyd CM, Hessel EM: **Functions of T cells in asthma: more than just T(H)2 cells.** *Nat Rev Immunol* 2010, **10**:838-848.
This review discusses the roles of different T cells subsets involved in allergic airway disease and describes how these cells might be manipulated for new asthma therapies.
49. An SS, Bai TR, Bates JH, Black JL, Brown RH, Brusasco V, Chitano P, Deng L, Dowell M, Eidelman DH *et al.*: **Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma.** *Eur Respir J* 2007, **29**:834-860.
This review discusses the central role of airway smooth muscle in the pathogenesis of airway hyperresponsiveness in asthma and highlights some important questions that remain to be answered.
50. Lambert RK, Wiggs BR, Kuwano K, Hogg JC, Paré PD: **Functional significance of increased airway smooth muscle in asthma and COPD.** *J Appl Physiol* 1993, **74**:2771-2781.
51. James AL, Wenzel S: **Clinical relevance of airway remodelling in airway diseases.** *Eur Respir J* 2007, **30**:134-155.
This review provides an excellent summary of accumulated knowledge in the area of airway tissue remodeling with special focus on clinical relevance in asthma and chronic obstructive pulmonary disease.
52. McParland BE, Macklem PT, Paré PD: **Airway wall remodeling: friend or foe?** *J Appl Physiol* 2003, **95**:426-434.
53. Brown RH, Mitzner W, Wagner EM: **Interaction between airway edema and lung inflation on responsiveness of individual airways in vivo.** *J Appl Physiol* 1997, **83**:366-370.
54. Grainge CL, Lau LCK, Ward JA, Dulay V, Lahiff G, Wilson S, Holgate S, Davies DE, Howarth PH: **Effect of bronchoconstriction on airway remodeling in asthma.** *N Engl J Med* 2011, **364**:2006-2015.
This study demonstrated that bronchoconstriction without additional inflammation induces airway remodeling in patients with asthma. The investigators suggest that treating inflammation is important but bronchoprotection is also important to prevent the long-term adverse consequences of airway remodeling.
55. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD: **Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years.** *Lancet* 1999, **354**:541-545.
56. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee WM, Shult PA, Reisdorf E *et al.*: **Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children.** *Am J Respir Crit Care Med* 2008, **178**:667-672.
57. Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchel EF, Gebretsadik T, Hartert TV: **Evidence of a causal role of winter virus infection during infancy in early childhood asthma.** *Am J Respir Crit Care Med* 2008, **178**:1123-1129.
58. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM: **Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life.** *Thorax* 2010, **65**:1045-1052.
59. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, Jeffery PK: **Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers.** *Am J Respir Crit Care Med* 2007, **176**:858-864.
This study provides the first histopathological evidence of reticular basement membrane thickening, a characteristic feature of asthmatic airway remodeling, in preschool children with documented wheezing. The results show that this remodeling develops between the ages of 1 and 3 years in wheezing preschool children.
60. Turato G, Barbato A, Baraldo S, Zanin ME, Bazzan E, Lokar-Oliani K, Calabrese F, Panizzolo C, Snijders D, Maestrelli P *et al.*:

Nonatopic children with multitrigger wheezing have airway pathology comparable to atopic asthma. *Am J Respir Crit Care Med* 2008, **178**:476-482.

This study shows that nonatopic children with multi-trigger wheezing have airway pathology typical of asthma that is undistinguishable from that seen in children with atopic wheezing.

61. Dakhama A, Lee YM, Gelfand EW: **Virus-induced airway dysfunction: pathogenesis and biomechanisms.** *Pediatr Infect Dis J* 2005, **24**:S159-S169.
62. Stein RT, Martinez FD: **Respiratory syncytial virus and asthma: still no final answer.** *Thorax* 2010, **65**:1033-1034.