corticosteroids) would seem to be the most appropriate treatment for EIB.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900QQ

Induction and Inhibition of the Th2 Phenotype Spread: Implications for Childhood Asthma

PURPOSE OF THE STUDY. T-helper 2 (Th2) phenotype spread refers to the concept that an established antigen-specific Th2 immune response may promote a Th2 response to a neoantigen. This study used a mouse model to investigate the requirements for induction and inhibition of phenotype spread to ragweed, a clinically relevant allergen.

METHODS. To induce and characterize phenotype spread, BALB/c mice were first immunized by a series of subcutaneous injections of egg ovalbumin and then challenged intranasally with ovalbumin, ragweed, or both simultaneously. Mice were finally challenged intranasally with ragweed alone to assess allergic response (Th2-mediated lung inflammation, ragweed-specific immunoglobulin E). To study the effect of time interval between the first and second antigens, the above-described experiment was repeated with ragweed being given either simultaneously with ovalbumin or 8, 24, or 48 hours after ovalbumin challenge. To investigate the role of activated Th2 cells in the induction of phenotype spread, severe combined immunodeficient (SCID) mice received ovalbumin-specific Th2 cells and naive CD4+ T cells intravenously and were initially challenged with ovalbumin and ragweed and then challenged later with ragweed and assessed for allergic response. To evaluate whether trafficking of naive CD4+ T cells to bronchial lymph nodes is required for the induction of phenotype spread, these cells were labeled and treated with an inhibitor of chemotaxis before the adoptive transfer experiments in the SCID mice. The effect on phenotype spread of immunostimulatory sequence-oligodeoxynucleotide (ISS-ODN), a Toll-like receptor 9 (TLR9) agonist, was first assessed in BALB/c mice by using the protocol described above, with injection of ISS-ODN before intranasal ovalbumin and ragweed challenge. ISS-ODN was also tested in the SCID adoptive-transfer model to study its effect on trafficking to regional lymph nodes.

RESULTS. The experiments yielded the following results: (1) Th2 phenotype spread to the neoallergen (ragweed) was induced only within the first 8 hours after bronchial challenge with the first antigen (ovalbumin); (2) the differentiation of naive CD4+ T cells to Th2 cells required trafficking of naive CD4+ T cells to bronchial lymph nodes and required interleukin-4 produced by ovalbumin-activated Th2 cells; and (3) a TLR9 agonist inhibited phenotype spread and experimental asthma by decreasing the production of chemokines involved in the trafficking of activated Th2 and naive CD4+ T cells to regional lymph nodes.

CONCLUSIONS. Th2 phenotype spread is the mechanism by which allergic sensitization to inhaled allergens is expanded in an already Th2-primed host. It occurs in regional lymph nodes and is mediated by interleukin-4 produced by activated Th2 cells.

REVIEWER COMMENTS. Studies have suggested that initial exposure to aeroallergens, the development of Th2 memory against them, and the associated clinical allergic manifestations occur during early childhood. Th2 phenotype spread may be the mechanism by which the allergic/asthmatic phenotype develops in early childhood. This study offers an animal model for further study of the inhibition of Th2 phenotype spread, which may lend insight to immunomodulatory interventions that could curb phenotype spread in early childhood, thereby attenuating or halting the allergic march.

Self-Organized Patchiness in Asthma as a Prelude to Catastrophic Shifts

PURPOSE OF THE STUDY. To reveal self-organized small airway constriction contributing to large ventilation defects in asthmatics.

STUDY POPULATION. Mild and moderate asthmatics.

METHODS. Ventilation defects in asthmatics were studied during methacholine bronchoprovocation by using serial dynamic positron emission tomography with a positron-emitter nitrogen-13 tracer and a single terminal-airway model.

RESULTS. Heterogeneity of ventilation defects in asthmatics was demonstrated. In this model, constriction of terminal bronchioles was the main feature of bronchoconstriction, contributing to nonuniform ventilation defects. Consequently, on the basis of the mechanical interdependence in expansion between airways and surrounding parenchyma, clusters of constricted terminal bronchioles fed by a common tree branch developed and led to large ventilation defects.
CONCLUSION. Clustered groups of self-organized terminal bronchiolar constriction, not large airways obstruction, contribute to large ventilation defects in acute asthma.

REVIEWER COMMENTS. The nature of functional changes of both small and large airways affecting ventilation during acute asthma attacks has been unclear. Previously, MRIs of asthmatic lungs during bronchoprovocation suggested large-airway obstruction as a major cause of large ventilation defects (eg. J Allergy Clin Immunol. 2003;111: 1205–1211). In this study, Venegas et al demonstrated the role of clustered terminal bronchiolar constriction resulting in ventilation defects in acute asthma. On the basis of this model, inhaled bronchodilators could be ineffective because the inhaled form might reach only well-ventilated regions and could further impede lung expansion of problematic regions and exacerbate regional ventilation defects. The concept of catastrophic shifts might account for sudden, unexplained, and severe asthma attacks in some patients. Systemic bronchodilators may be needed in some asthmatics to bypass this problem. This line of investigation is further elucidated elsewhere (J Appl Physiol. 2005;99:2388–2397).

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900SS

Akaluck Thatayatikom, MD
Bangkok, Thailand

Andrew H. Liu, MD
Denver, CO

The Bronchial Lavage of Pediatric Patients With Asthma Contains Infectious Chlamydia

PURPOSE OF THE STUDY. To examine the frequency of Chlamydia pneumoniae infections in pediatric patients with asthma.

STUDY POPULATION. Seventy pediatric patients undergoing flexible fiber-optic bronchoscopy as a part of their ongoing clinical care.

METHODS. Bronchoaveolar lavage (BAL) fluid and blood were examined for the presence of C pneumoniae by smear examination and culture. The BAL and blood samples were cultured on human or mouse macrophages to determine infectivity. Polymerase chain reaction (PCR) amplification of BAL samples was performed to confirm specificity of the culture technique. Blood was examined for total immunoglobulin E (IgE). Blood samples from 70 matched, nonrespiratory control patients were cultured for Chlamydia.

RESULTS. Forty-two patients undergoing bronchoscopy had asthma and 28 had various other respiratory diseases. Thirty-eight (54%) BAL samples were positive for Chlamydia by PCR and 22 (31%) samples were positive for Chlamydia by culture. Of the positive BAL samples, 28 (74%) of 38 PCR-positive and 14 (64%) of 22 culture-positive samples were from children with asthma. Culture-positive blood samples were found in 24 (34%) of 70 respiratory patients and 8 (11%) of 70 nonrespiratory controls. In the blood culture–positive respiratory group, 17 (71%) of 24 were from children with asthma. Elevated total serum IgE was associated with BAL culture–positive results, and this relationship was stronger than total IgE and asthma diagnosis.

CONCLUSIONS. Viable C pneumoniae organisms are frequently present in the lung lavage in a cohort of predominately asthmatic pediatric patients.

REVIEWER COMMENTS. Results from this study suggest that infectious C pneumoniae may be common in BAL fluid of children with asthma. Historically, C pneumoniae has been associated with exacerbation and increased incidence of respiratory conditions in adults, but studies to examine similar associations in children have not been performed. This is the first investigation to report viable and infectious C pneumoniae in the BAL fluid of children with asthma. These findings are intriguing and should encourage investigators to examine the clinical implications of Chlamydia infection among pediatric patients with asthma.

Repeat Exercise Normalizes the Gas-Exchange Impairment Induced by a Previous Exercise Bout in Asthmatic Subjects

PURPOSE OF THE STUDY. To determine the effects of a second exercise bout on the gas-exchange impairment caused by an initial exercise-induced bronchospasm (EIB) response in asthmatic subjects.

STUDY POPULATION. Twenty-one subjects with a known history of asthma participated after meeting at least 1 inclusion criteria: (1) ≥12% increase in the forced expiratory volume in 1 second (FEV1) after β-agonist inhalation, (2) ≥10% decrease in FEV1 after exercise test to exhaustion, or (3) a provocative concentration ≤4.0 mg/mL of methacholine causing a 20% decrease in FEV1.

METHODS. The subjects performed 2 submaximal workloads for 3 minutes. After 3 to 5 minutes of rest, constant work-rate exercise was performed until exhaustion at 90% of maximal O2 uptake (EX1). Arterial blood and expired gases were collected at 3 (early recovery) and 35 (late recovery) minutes after EX1. Subjects then per-
Self-Organized Patchiness in Asthma as a Prelude to Catastrophic Shifts
Akaluck Thatayatikom and Andrew H. Liu
Pediatrics 2006;118;S27
DOI: 10.1542/peds.2006-0900SS

Updated Information & Services
including high resolution figures, can be found at:
/content/118/Supplement_1/S27.1

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2006 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™
Self-Organized Patchiness in Asthma as a Prelude to Catastrophic Shifts
Akaluck Thatayatikom and Andrew H. Liu
Pediatrics 2006;118:S27
DOI: 10.1542/peds.2006-0900SS

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/118/Supplement_1/S27.1