UPMC’s Asthma Institute at the University of Pittsburgh School of Medicine was founded in 2009. It is a joint venture among the Department of Medicine, the Division of Pulmonary, Allergy, and Critical Care Medicine, Children’s Hospital of Pittsburgh of UPMC, and the Pediatric Environmental Medicine Center.

The Asthma Institute is directed by Sally Wenzel, MD, who is ranked as one of the top 10 asthma specialists in the world*. Dr. Wenzel has a passion for understanding and improving the treatment of asthma, in particular severe asthma. She served as chair of the International American Thoracic Society/European Respiratory Society Guidelines on severe asthma. Dr. Wenzel is one of seven doctors in the Severe Asthma Research Program (SARP) network funded by the National Heart, Lung, and Blood Institute. Through SARP and her own efforts, Dr. Wenzel has accumulated a clinical database of nearly 700 patients with asthma and individuals who do not have an asthma diagnosis, most of whom have matching airway tissue, cells, and sputum/lavage. Her lab is one of very few labs in the world able to match clinical characteristics of a patient with responses at a cellular/molecular level. Her current interests include the role of epithelial cells in controlling airway inflammatory responses, as well as their interactions with mast cells. She was the first author on a recent *New England Journal of Medicine* paper that described perhaps the most promising results for a new asthma drug in decades.

In this issue, Dr. Wenzel and her team at the Asthma Institute will highlight some of the newest approaches to clinical therapies and research results to assist in patient treatment.

(Continued on Page 2)
The Asthma Institute (continued)

We welcome any suggestions or comments on how we might support you in the care of your patients. Please enjoy this issue of Respiratory Reader.

With great enthusiasm and respect,

Mark T. Gladwin, MD
Professor of Medicine
Chief, Pulmonary, Allergy, and Critical Care Medicine
Director, Vascular Medicine Institute

Sally Wenzel, MD
Professor of Medicine
Director, University of Pittsburgh Asthma Institute at UPMC/UPSOM

*According to expertscape.com.

Educational Opportunities

PACCM is deeply committed to a mission that includes:

- Providing the highest-quality, compassionate patient care for patients with lung disease.
- Mentoring and training medical students, residents, fellows, and young faculty.
- Research and scientific discovery.

To foster an educational and collaborative environment, the division offers the following weekly conferences throughout the academic year:

Basic and Translational Research in Lung Disease Conference is held every Tuesday from noon to 1 p.m. in the Biomedical Science Tower, Conference Room 1295. This conference provides pulmonary faculty and staff an opportunity to hear speakers from throughout the university outline their current biomedical research efforts in order to facilitate expanded collaborations.

Pulmonary Case Conference is held every Thursday from noon to 1 p.m. in the Biomedical Science Tower, Conference Room 1295.

Pulmonary Grand Rounds is held each Friday from noon to 1 p.m. in UPMC Montefiore, Conference Room, NW628. It consists of lectures by external and internal speakers and is designed to bring forth the latest scientific and clinical developments in pulmonary and allergic diseases.

If you wish to be placed on our email distribution list, please contact Theresa Dobransky at dobranskyta@upmc.edu.

To learn more about our additional educational resources, including free CME videos and podcasts, visit UPMCPhysicianResources.com/Pulmonology.

How to Refer a Patient for Lung Transplant Evaluation

To refer a patient for lung transplant evaluation, the following information is needed:

- Patient’s name and contact information
- Date of birth
- SSN
- Insurance information
- Medical records, including an H&P, PFTs, CT scan, and CXR reports from the last two years, routine blood work results, current medication list, and any cardiac testing that has been done, such as an echo and/or left- and right-heart catheterization.

The information can be faxed or mailed to the attention of Nancy Pepke, BSN, RN, CCTC, intake coordinator:

Fax: 412-648-6369

Mailing address:
UPMC Presbyterian Lung Transplant Program
200 Lothrop St., Suite C-900
Pittsburgh, PA 15213

Insurance clearance can take up to two to three weeks. Once insurance authorization is received and medical records have been reviewed, the patient will be contacted for a phone interview/history. Once deemed acceptable for evaluation, the patient will be asked to provide a date when he or she AND a family member can come in for three to five days of testing. Referring physicians can request an expedited schedule for a patient based upon their assessment. If you have questions, please call the pretransplant office at 412-648-6202.

*According to expertscape.com.
Immunodeficiency Evaluation in Adults

By Andrej Petrov, MD

Although primary immunodeficiency (PI) diseases have typically been associated with the world of pediatrics, there is a growing appreciation that adults can also be affected by the PI disease. The advances in diagnosis and treatment of the childhood immunodeficiency diseases have allowed many children born with the PI disease to survive into adulthood. Additionally, several common PI diseases often present “de novo” in adulthood, causing significant morbidity. Furthermore, the advent of immunosuppressive treatments in autoimmune conditions and organ transplantation has opened the doors for acquired immunodeficiency conditions that can potentially mimic the clinical presentation of PI conditions.

Definition

The immunodeficiency diseases represent a group of disorders in which there is an impairment of the immune system causing an increased susceptibility to infections and noninfectious comorbidities that span many organ systems. These diseases are caused by hereditary or new genetic or acquired defects and can present at birth, early childhood, or adulthood. Traditionally, the type of infection is determined by whether the defect is located in cellular (lymphocytes, phagocytes, and neutrophils) or humoral (antibodies) immunity. Of note, many patients will have combined cellular and humoral immunity defects, making it harder to diagnose the type of immune deficiency based on their clinical presentation.

Clinical presentation

The clinical suspicion for primary immunodeficiency should arise if one encounters a patient with any of the following features: severe infections requiring a hospitalization, persistent infections or an infection caused by an uncommon organism, recurrent infections, or a family history of recurrent infections. For example, in our practice we diagnosed PI in a number of patients whose initial presentation was a life-threatening pneumonia or infections. Noninfectious phenotypes of PI may present as a chronic sinusitis, recurrent bronchial infections and bronchiectasis followed by diagnosis of PI.

The type of infection seen in PI can vary based on underlying disease. For example, the patients with IgA deficiency or common variable immunodeficiency (CVID) often present with recurrent sinopulmonary infections with encapsulated organisms, while the patients with chronic granulomatous disease commonly present with the infections caused by Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia and Nocardia.

We have also learned that many patients with PI may not present with infections. Noninfectious phenotypes of CVID, including autoimmune disease (idiopathic thrombocytopenic purpura, hemolytic anemia, etc.), granulomatous inflammation, lymphoid hyperplasia, or gastrointestinal disease may be presenting, coexistent, or sole manifestations of this immunodeficiency. Moreover, these noninfectious presentations of CVID can mimic other conditions, such as sarcoidosis, inflammatory bowel disease, or interstitial lung disease, leading to a significant impediment in diagnosis of CVID. Because these conditions mimicked by CVID often require immunosuppressive treatments, any delay in diagnosis and appropriate treatment of CVID may cause significant complications and increase the risk of an infection.

Diagnosis

The standard screening test for antibody deficiency starts with measurement of IgG, IgA, and IgM immunoglobulin levels in the blood serum. Occasionally, an IgE level will be checked if clinical features suggest the diagnosis of hyper-IgE syndrome. If clinically indicated, one can measure specific antibody production (also known as amnestic vaccine response) to better evaluate antibody function. The patient might need to be immunized with common vaccines, including those with protein antigens (such as tetanus toxoid, diphtheria toxoid) and carbohydrate antigens (such as Pneumovax®), and repeat serologic studies should be obtained approximately four to six weeks after the immunization.

The evaluation of cellular immunity focuses on determining the numbers of different types of B- and T-lymphocytes and evaluating the function of these cells. The initial test to evaluate possible decreased or absent lymphocytes is a complete blood count (CBC) and differential. Lymphopenia can be further analyzed by using flow cytometry to obtain lymphocyte subsets and, if needed, by measuring T-cell proliferation after mitogen stimulation.

Laboratory testing to diagnose chronic granulomatous disease relies on the evaluation of oxidative burst in neutrophils and macrophages. This can be measured by using a number of different methods including the nitroblue tetrazolium (NBT) test.

Many immune deficiencies are associated with specific genetic defects, and additional genetic studies might be needed to confirm the diagnosis of PI disease. Occasionally, complement studies will be ordered to rule out complement defects. Finally, the secondary causes of abnormal immune studies should be ruled out before making a diagnosis of PI disease.

Treatment

The patient with confirmed PI disease will often require prophylactic treatments to prevent infections or complications of infections (such as bronchiectasis) and immunosuppressive therapy to manage noninfectious manifestations. Some patients with an isolated decrease in IgG level and infrequent infections may not require treatment. The most common prophylactic treatments include immunoglobulin replacement therapy in humoral immunodeficiency conditions, interferon gamma in CGD, and/or prophylactic antibiotics in patients with humoral or cellular immunodeficiency. Once a diagnosis has been made, therapy will likely be lifelong. In some instances, reevaluation of the diagnosis may be undertaken by discontinuing therapy and retesting immune function.
Asthma is an important national health problem, affecting 6 to 8 percent of the U.S. population, with 10 percent of all asthmatics having severe disease and responding poorly to standard asthma treatment such as inhaled and systemic corticosteroids. The pathobiology of asthma involves many cell types, including the mast cell (MC), a resident inflammatory cell expressing CD34, c-kit, and the high affinity IgE receptor. Unfortunately, human mast cells remain difficult to study, because they are not present as circulating blood cells and bear little resemblance to primary cells.

Lab Spotlight: Severe Asthma Study Supports a Role for the Mast Cell and Prostaglandin D2 Pathway in Specific Asthma Phenotypes

By Merritt Fajt, MD

The National Institutes of Health National Heart, Lung, and Blood Institute awarded Severe Asthma Research Program (SARP) grants to seven leading asthma clinical university centers across the United States, including the University of Pittsburgh. The Pitt program is led by Sally Wenzel, MD, professor of medicine, director of the University of Pittsburgh Asthma Institute at UPMC and subsection chief of Allergy-Immunology in the Division of Pulmonary, Allergy, and Critical Care Medicine. She is a world-renowned translational researcher and expert in severe asthma. Merritt Fajt, MD, assistant professor of medicine, has been working with Dr. Wenzel using clinical and translational methods to focus on asthma phenotypes and their relation to mast cells in the airway in this challenging severe asthmatic population.

Mast cells have long been implicated in the pathogenesis of asthma through Type I hypersensitivity reactions, likely through activation of epithelial MCs. Studies in mice and humans suggest the environment is highly influential in determining the cell phenotype. In humans, the tissue environment is believed to contribute to two major MC phenotypes, identified by their protease-rich cytoplasmic granule content. The MCT contains tryptase and is thought to represent a mucosal MC phenotype. Under normal circumstances, the MCT represents the majority of lung MCs. (Figure 1, tryptase positive MCs in the epithelial brushing from a severe asthmatic.) In contrast, the MCTC phenotype is identified by chymase and smaller amounts of tryptase, and has been proposed to contain carboxypeptidase A3 (CPA3) and hematopoietic prostaglandin D synthase (HPGDS). HPGDS is the enzyme that generates prostaglandin D2 (PGD2), which acts on three G-protein coupled receptors, including chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTH2) and DP1. CRTH2 has been of significant interest as a therapeutic target in asthma. However, much remains to be understood regarding the presence and activation of these pathway elements in asthma.

Their research team has shown that the presence and activation of MCs in chronic severe asthma differs from milder asthma, with severe asthmatic airways having higher percentages of MCTC than milder asthma. This increase in epithelial MCs is associated with increases in bronchoalveolar lavage fluid PGD2.

Building on this novel finding, Dr. Fajt’s recent work, published in The Journal of Allergy and Clinical Immunology, compared the expression and activation of PGD2 pathway elements in bronchoscopically obtained samples from 107 participants, healthy controls and asthmatics, across a range of severity and control. Dr. Fajt also explored the PGD2 pathway in relationship to a phenotype of asthma with evidence for a T-helper type 2-like inflammation. Confirming their previous results, BAL fluid PGD2 was highest in severe asthma. Bronchial epithelial brushing HPGDS mRNA and cells staining positively for HPGDS protein differed among the groups.

Figure 1: Bronchial epithelial brushing cells stained for tryptase from a severe asthmatic. Red arrows: Tryptase-positive mast cells.
This past November, during Pulmonary Hypertension Awareness Month, the Pulmonary Hypertension Association reached out nationwide to raise awareness about a potentially curable form of pulmonary hypertension: chronic thromboembolic pulmonary hypertension (CTEPH). UPMC joined in this call to raise awareness about CTEPH. The greatest risk factor for developing CTEPH is history of pulmonary embolism, affecting as many as 3.8 percent of patients who survive pulmonary embolism (PE)(1). However, in a cohort of 500 patients with CTEPH, as many as 30 percent had no known history of pulmonary embolism (2). These data reinforce to us the importance of close follow-up of patients after PE so that in those affected, we can make an early diagnosis and potentially cure CTEPH with pulmonary thromboendarterectomy. Furthermore, it also reinforces the importance of screening newly diagnosed PAH patients for CTEPH using the most sensitive modality: ventilation/perfusion scanning.

At UPMC, we are happy to help in the evaluation and management of patients who have PAH in our Comprehensive Pulmonary Hypertension Program. In addition to our cardiothoracic surgery team, we incorporate a medical team of pulmonologists, cardiologists, and hematologists to provide the most thorough medical and surgical care possible in this patient population.

We welcome referrals to our clinic of patients who have had PE, consultations for patients in whom pulmonary hypertension or CTEPH is suspected, and most of all, the opportunity to work with referring physicians to establish a care plan that best assures complete resolution after PE and treatment of pulmonary hypertension. To make a referral to the CTEPH program, please call 1-800-PH4-UPMC (8762).

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

By Patricia George, MD

These studies suggest a highly active PGD2 pathway in poorly controlled severe asthma patients. Several recent studies, including one presented at the recent American Academy of Asthma, Allergy and Immunology meeting, have shown that CRTH2 antagonists improve lung function and asthma control, and may decrease exacerbations in milder asthma (Wenzel, AAAAI poster, 2014). Dr. Fajt’s recent studies in severe asthma, in conjunction with these early therapeutic trials, support the need for trials of CRTH2 antagonists in severe asthma. The research team at the Asthma Institute continues to enroll asthmatics in the SARP study, as well as in numerous other asthma clinical trials that will lead to better understanding of the role of the MC and its mediators in human asthma.
Putting “The Science” Into Asthma Treatment: New Immunologic Approaches to Asthma

By Sally Wenzel, MD

In the last 30 years, treatment of asthma has centered on the use of corticosteroids, both inhaled and by mouth. These treatments led to substantial improvements in asthma symptoms and attacks, and an overall decline in deaths from asthma. However, it is also recognized that a substantial group of asthmatics remain who do not respond fully to this treatment and whose asthma remains difficult to treat. Patients who do not fully improve with standard asthma medications have been targeted for development of new classes of drugs called “biologic” therapy. These therapies are called antibodies, and they are directed at certain body chemicals.

It is increasingly recognized that asthma, and more severe asthma in particular, is not a single disease, but rather consists of several subtypes. This is similar to the multiple types of arthritis that are recognized, most of which respond differently to different treatments. One of main differentiating features in asthma has been the presence or absence of a particular type of inflammation, called a Th2-like inflammation. It is likely that about half of all asthma consists of this type of inflammation. In both mice and humans, this inflammation has been associated with marked changes in the lung, including increased mucus production, increases in cells called eosinophils, and even scarring. In both mice and humans, there is evidence that these changes may be due to increases in certain chemicals in the body called “Th2 cytokines.” These chemicals have become the target of specific immunologic therapies for those patients with “Th2-like asthma.

**Biologic therapies for Th2-like asthma**

There are now two different categories of therapies for this type of asthma. Each of these uses an approach which makes antibodies that target and remove chemicals, called cytokines, from the body. These cytokines, Interleukin (IL)-4, -5 and -13, are made in high amounts by these Th2-like asthma patients. The antibodies that are furthest along in development are antibodies to IL-5. Very large studies with hundreds of people have shown that patients with more severe asthma who have slightly raised levels of eosinophils in their blood or lungs had a reduction in asthma attacks that required prednisone treatment when treated with these antibodies. Since exacerbations of asthma can be very uncomfortable, cause trips to receive urgent health care, and even cause death, a 50 percent reduction is a highly meaningful outcome. People who get their asthma as adults, and those with nasal polyps, may do particularly well.

The second category of therapies is those that block the ILs -4 and -13, either alone, or in combination. The antibody against IL-13, lebrikizumab, is furthest along in this category and has shown an ability to improve lung function and to possibly decrease asthma attacks as well, but again, specifically in patients with evidence for Th2-like asthma. A very recent study of an antibody which blocks both IL-4 and IL-13 is perhaps the most exciting. This early stage study, also recently published in The New England Journal of Medicine, shows the broadest and most significant range of improvements in asthma related outcomes of any new therapy to date. In patients with slight elevations in blood eosinophils (which can be measured in a simple test called a complete blood count or CBC), an antibody called dupilumab, when added to therapy with long-acting beta agonists and inhaled corticosteroids (drugs like Advair®, Symbicort®, and Dulera®) still improved many asthma related outcomes. Dupilumab improved asthma symptoms (the first of the new classes of drugs to do that), decreased need for rescue medication, and improved lung function tests. These effects were seen on top of the background use of the traditional asthma medications mentioned above. But in addition, when the background medications were discontinued or tapered off, the improvements were maintained on dupilumab, while symptom and rescue medication use increased on the “placebo” (sugar pill, or in this case, injection). In fact, nearly half of the patients treated with placebo actually developed a limited/controlled asthma attack, while only 5 percent of the dupilumab-treated patients did.

**Biologic treatments for “non-Th2” asthma**

While substantial progress has been made in Th2-like asthma, very little progress has been made in the other half of asthma patients. This group is poorly understood, and considerably more research is required to find therapies. Some studies are continuing with an antibody directed toward IL-17-related inflammation. Early studies showed some effect on lung function and symptoms, but only in patients with a very big improvement in lung function after their short-acting bronchodilator/rescue medication. Much more work is needed in this area.

**Conclusions**

Considerable progress has been made in the development of new and novel approaches for the treatment of Th2-like asthma. The combination of the ability to identify these patients on the basis of simple blood tests, including blood eosinophils, is allowing us to bring the right drug to the right patients to personalize and improve their therapy.
Team PHenomenal Hope Returns to Race in 2015

UPMC is proud to announce its 2015 partnership with Team PHenomenal Hope, a charity cycling team that raced with the Pulmonary Hypertension Association (PHA) from Oceanside, California to Annapolis, Maryland in the Race Across America (RAAM) 2014.

A new look and new goals in 2015
Team PHenomenal Hope (Team PH) will expand from a team of four cyclists to a larger endurance/ultra-endurance team. The team currently consists of 12 athletes from western Pennsylvania and eastern Ohio, with ultra-cyclists, marathon and ultra-runners, ultra-swimmers, and Ironman® triathletes, and captained by Team PH veteran Ryanne Palermo. Each month, the team will be racing in high profile events, from 24-hour cycling races to Ironman triathlons, and Race Across the West in June.

The athletes share a passion for endurance sports, as well as a desire to inspire people to make a difference in the lives of people living with pulmonary hypertension. “We have some exciting events coming in 2015,” stated team manager and pulmonary hypertension (PH) doctor Patricia George. “I am most excited about the growth and new direction of this team. Our goal in 2015 will be to broaden our reach, raising awareness and flying PH colors in races throughout the year all over the map,” she said.

“Not only did we feel the excitement and satisfaction of completing the Race Across America,” George said, “but truly knew that this was the effort of the PH community at large. It was that driving force, that excitement of racing with the vibrant PH community that I will never forget. It is that same positive vibe that we look to build upon as Team PHenomenal Hope grows in 2015.”

Save the Date: Spring 2015 Clinical Conference –
Topics in Pulmonary Medicine: Management of Acute and Chronic Pulmonary Embolism

Friday, March 20, 2015 – LHAS Auditorium, UPMC Montefiore

Course Co-directors:
Patricia George, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
Belinda Rivera-Lebron, MD, MS
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine

The goal of this conference is to provide up-to-date information about advancements in the field of pulmonary embolism, as well as management of PE complications such as pulmonary hypertension and CTEPH.

Topics will include:
- Natural history of the pulmonary thromboembolism
- Management of submassive PE – special considerations
- Novel therapies including catheter-directed thrombolysis, hypercoagulable states and newer oral anticoagulants
- Long-term complications of acute PE: CTEPH
- Surgical treatment of CTEPH: pulmonary thromboendartarectomy

Who Should Attend
Healthcare providers who take care of patients with pulmonary embolism and/or pulmonary hypertension.

This activity has been approved for AMA PRA Category 1 Credit(s)™
The University of Pittsburgh is an affirmative action, equal opportunity institution.

Presented By:
University of Pittsburgh School of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
and the
University of Pittsburgh School of Medicine
Center for Continuing Education in the Health Sciences.

Seating is limited, registration is required.

For more information, please visit the conference page on UPMC Physician Resources at: UPMC.com/PEconference.
Can Changes in the Diet Make a Difference in Asthma?

By Fernando Holguin, MD

It is widely accepted that obesity adversely affects the respiratory health of people with asthma and that losing weight improves symptoms and lung function for the majority of obese or overweight asthmatics. Yet, it is unclear whether controlling dietary intake beyond the goal of achieving a healthy body mass index (BMI) can clinically influence asthma control or exacerbation rates. There are many nutritional components, which at least intuitively, make sense as having beneficial effects on asthma. Topping the list is vitamin D, which has been the focus of many asthma studies. In observational studies, lower levels of vitamin D have been associated with lower levels of FEV1, greater respiratory symptoms, increased risk of exacerbation, and poorer control. Although not fully understood, reduced vitamin D levels could adversely affect asthma by enhancing susceptibility to respiratory infections and impairing the response to corticosteroids. The National Institutes of Health AsthmaNet study, of which the University of Pittsburgh is a part, has just completed the first randomized clinical trial of vitamin D supplementation for adults with asthma with insufficient vitamin D levels. These results will be pivotal in determining what role vitamin D supplementation should have in the treatment of asthmatics.

Because airway inflammation has been associated with increased oxidative stress and reduced plasma levels of nonenzymatic antioxidants such as D-carotene, vitamin C, or vitamin E have been related to lower FEV1 levels, these compounds have been extensively studied as potential therapeutic agents for asthma and other obstructive airway diseases. Compared with healthy control subjects, patients with asthma have lower plasma levels of carotenoids, ascorbic acid, and vitamin E. Reduced ascorbic acid levels have been associated with increased respiratory symptoms, higher odds of being diagnosed with asthma, and diminished lung function, whereas lower plasma carotene levels have also been associated with higher odds for asthma diagnosis. However, supplementation with these compounds has not consistently been shown to reduce respiratory symptoms or improve lung function. This potentially suggests that supplementation might only be useful in a subset of asthmatics. Some of these groups may include children with asthma chronically exposed to high ground ozone levels from air pollution and with specific polymorphisms, such as the glutathione S-transferase M1 or GSTM1. Children with this null genotype (allele frequency of 40 percent in the general population) are more susceptible to ozone exposure and have been shown to be protected by antioxidant supplementation from vitamins C and E. Other specific populations that could benefit from supplementation are heavy smokers with low vitamin C, and particularly those with functional polymorphisms in the glutamate-cysteine ligase, which are at highest risk from accelerated lung function decline.

It has been hypothesized that the increased burden of asthma and allergies seen in more industrialized societies may be related to a progressive intake of n-fatty acids, such as linoleic acid, which is in margarines and vegetable oils, and a lower intake of n-3, which is found predominantly in marine oils. This concept may partly explain why the prevalence of asthma and allergies is lower among Inuit populations. Given that the incorporation of n-3 fatty acids into cell membranes leads to less pro-inflammatory mediators, and because its downstream metabolites have the potential to resolve inflammation, the use of n-3 fatty acids as nutritional supplements to improve asthma seems plausible. However, observational studies have not shown a consistent association between having low n-3 levels with improved lung function or reduced respiratory symptoms. Several randomized studies have been conducted looking at a variety of outcomes and have also not shown consistent benefits. A pooled analysis of nine studies by the Cochrane group revealed no improvements in clinical outcomes, including bronchial hyperresponsiveness. This led to the conclusion that there is currently insufficient evidence to recommend n-3 fatty acids to improve the respiratory health of persons with asthma. However, n-3 fatty acids may have a role in specific asthma phenotypes, such as exercise-induced asthma, where its supplementation has been shown to prevent exercise-mediated reduction in FEV1 and use of rescue inhalers. Among atopic asthmatic patients, n-3 fatty acid supplementation has been shown to reduce exhaled nitric oxide levels and sputum eosinophil counts in asthmatic patients pre-exposed to sensitized allergens; however, these results have not been widely replicated.

In summary, there is some scientific rationale to supplement subjects with asthma with nonenzymatic antioxidants, higher n-3 fatty acids, and vitamin D. However, clinical and observational studies do not strongly support their use in clinical practice. Although there might be specific asthma phenotypes that would benefit more greatly from this type of dietary manipulation, we don’t have a way to identify who these phenotypes are. So, for now, the only sensible recommendation for diet and asthma is to maintain a balanced diet and a healthy weight.
A 26-year-old female with a past medical history of anxiety disorder presented for evaluation of a three-month history of daily generalized pruritic hives intermittently associated with lip and periorbital swelling. She did not have symptom-associated fevers, joint pain, shortness of breath, or painful or bruising urticaria. She was not taking any new medications, and did not have any known food or medication allergies. She had a family history of Hashimoto’s disease. Examination revealed diffuse red wheals without dermatographism.

Chronic urticaria is present when hives occur regularly for greater than six weeks. Hives can occur alone in 40 percent of patients, with angioedema in 40 percent of patients, or in 20 percent of cases, angioedema can occur alone. Angioedema affects the lips, face, hands, feet, or scrotum. Angioedema can affect the pharynx and tongue, but almost never involves the larynx.

Chronic urticaria is often idiopathic; however, other etiologies should be considered, including dermatographism and physical urticaria (e.g., cold, cholinergic, pressure, vibratory, solar, and aquagenic), or autoimmune (40 to 45 percent of patients have circulating IgG antibodies directed against the IgE receptor or IgE). Additionally, in a subset of patients, urticaria and angioedema can be a manifestation of an underlying connective tissue disease, systemic vasculitis, or thyroid disease.

A thorough history and physical examination assesses for symptoms/signs that may indicate vasculitis or other connective tissue disease. If evaluation is not suggestive of an underlying systemic condition, routine laboratory testing is not indicated. If systemic disease is suspected, testing includes erythrocyte sedimentation rate, antinuclear antibodies, thyroid antibodies, or skin biopsy. Hereditary angioedema is not associated with urticaria; therefore, in patients with urticarial, testing of complement or C1 inhibitor is not indicated.

The mainstay of treatment includes use of nonsedating antihistamines such as fexofenadine or cetirizine. However, in severe cases, the usual recommended dose of antihistamines may not be beneficial. Therefore, use of doses as high as four times the standard dose is indicated in these patients and has been shown to be effective.

In recalcitrant disease, other treatments are added in a step-wise manner to achieve remission. Following maximal doses of nonsedating antihistamines, the addition of a first-generation sedating antihistamine (e.g., hydroxyzine or doxepin) or H2 receptor blockade (e.g. ranitidine) is considered. Approximately 15 percent of histamine receptors in the skin are H2 subtype, and therefore, the addition of H2 blockade can augment inhibition of the wheal-and-flare reaction. If urticaria persists despite maximal histamine blockade, other therapeutic options include: leukotriene receptor antagonists, long-term corticosteroids, and steroid sparing agents such as colchicine, sulfasalazine, hydroxychloroquine, dapsone, mycophenolate, cyclosporine, and omalizumab.

The patient was started on fexofenadine 360 mg twice daily (four times standard dose) without change in urticaria. In a step-wise manner, doxepin 10 mg at bedtime was started followed by ranitidine 150 mg twice daily without a change in her symptoms. Given her family history of thyroid disease, an evaluation of TSH and thyroid antibodies revealed a diagnosis of Hashimoto’s disease, and she was started on thyroid replacement with gradual improvement of urticaria and angioedema. Currently, antihistamines are being reduced as tolerated by her symptoms.
New Clinical Trials: Exciting developments in asthma research and care, and ways asthmatics can participate.

A centerpiece of the Asthma Institute is Volunteer for Asthma — AIR (Asthma Institute Research Registry). It is a program for adults with asthma, from the mild to most severe patients, who wish to be notified about new research studies for which they may qualify. AIR volunteers have enabled the Asthma Institute to be a national leader in the discovery of new asthma treatments. If you are 18 years of age with a current diagnosis of asthma and a non-smoker, please consider joining today! No more than an hour-and-a-half of your time is needed to join. Compensation and parking are provided. For more information or to join Volunteer for Asthma — AIR, call 1-866-804-5278 or email asthmainstitute@upmc.edu.

Current Clinical Trials
There are several clinical trials at the Asthma Institute. Some are investigating innovative ways to treat asthma by focusing on eosinophils, or inflammation of the airways. Other studies examine different contributing factors, such as obesity. All studies require patient information related to health and asthma history, as well as lung function. The Asthma Institute is especially interested in improving the lives of people with severe or difficult to treat asthma. These studies benefit participants and asthma sufferers all over the world. By discovering how asthma works, we can work to advance asthma treatment. Information gathered from these studies not only helps the Asthma Institute develop a better understanding for the treatment of asthma, the data is also used by other collaborative centers all over the nation. All of the medicines we currently have for asthma treatment were developed through clinical trials. To further our research and continue discovering treatments, we need participants!

Contact the Comprehensive Lung Center
Comprehensive Lung Center
Falk Medical Building
3601 Fifth Ave., Fourth floor
Pittsburgh, PA 15213

Phone: 412-648-6161
Toll-free: 1-800-248-LUNG (5864)
Fax: 412-648-6869
Email: asthmainstitute@upmc.edu

BARD (NIH-funded) — Goal is to find the best asthma treatment to add for African-American people who have asthma that is not well-controlled on low doses of inhaled steroids. There are 15 to 18 study visits over the period of about one year and four months. Participants will receive four study treatments (ICS and ICS/LABA) across four 14-week treatment periods.

SARP III (NIH-funded) is a longitudinal study; recruiting asthmatics of all severities to improve the understanding of severe asthma. The study involves visits over four to six week period plus follow-up.

SANDIA — this study is looking at the possibility that the supplement L-Citrulline may improve nitric oxide levels in the airways. The study involves 14 days or three office visits.

SANOFI — A double-blinded, placebo-controlled study of dupilumab for adults with moderate to severe uncontrolled asthma. Duration is 43 weeks, consisting of 18 study visits. Four possible doses or placebo given via injection every two weeks.
2014 Pittsburgh-Munich Lung Conference

The Pittsburgh-Munich Lung Conference took place on October 23 and 24, 2014. It was the first conference co-hosted with the Comprehensive Pneumology Center of Munich, Germany. The topic of this year’s conference was, “Aging and Lung Disease: Clinical Impact and Cellular and Molecular Pathways.” The conference was held at the University Club in Oakland and proved to be the most well-attended conference to date, with more than 300 national and international attendees.

The conference opened with a presentation by Kevin P. High, MD, MS, chief of Infectious Diseases and interim chair of the Department of Internal Medicine at Wake Forest School of Medicine, summarizing the relevance, challenges, and impact of the clinical research in aging, followed by 26 speakers in six symposia:

- The role of mitochondria, telomeres, and telomerase and the critical role of extracellular matrix in the pathogenesis of age-related lung diseases and familial IPF.
- Molecular drivers of cell aging and their impact in the respiratory system.
- Recent advances in the genetic, metabolic, and proteomic technology to assess aging.
- The relation of age and lung diseases including chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and acute respiratory distress syndrome (ARDS).
- The implication of cellular senescence and the epigenetic changes.
- The adaptations to cell stress and aging on mesenchymal stem cells, endothelial cells, and lung epithelial cells.

Speakers included MDs and PhDs from academia, governmental organizations, and industry, and highlighted both clinical updates and cutting-edge research. Each symposium concluded with a panel session with all speakers and the audience. There was also a poster session and reception with more than 60 posters, followed by a banquet dinner at Phipps Conservatory and Botanical Gardens. This year’s speaker was Brian Kennedy, PhD, CEO of the Buck Institute for Research on Aging, who spoke on “Aging and Chronic Disease — A View From the Aging Side”. Look for summaries of the conference sessions in the *Annals of the American Thoracic Society* later this year.

Valerian Kagan, PhD, DSc, speaks at the 2014 Pitt-Munich International Lung Conference.

Oliver Eickelberg, MD, PhD (right), and course directors Mark Gladwin, MD (far left), Ana Mora, MD (left), and Mauricio Rojas, MD (far right), pose with this year’s poster winners.

Louis Vuga, MD, stands with his poster “VCAM1 Distinguishes Idiopathic Pulmonary Fibrosis (IPF) with and without Pulmonary Hypertension.”
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