In This Issue:
The Emphysema Research Center, Case Studies, Clinical Trials, and more

The Emphysema/COPD Research Center (ECRC), directed by Frank Sciurba, MD, FCCP, is a specialty center of the Division of Pulmonary, Allergy, and Critical Care Medicine at UPMC with the mission to advance our understanding of emphysema and tobacco-related lung disease and to evaluate new therapies for patients.

Chronic obstructive pulmonary disease (COPD) is a serious lung disease that causes breathing difficulty and can interfere with normal daily activities like walking, doing housework, or preparing meals. As the fourth-leading cause of death in the United States, more than 12 million people have COPD, and another 12 million likely have the disease but don’t know it.

What we now naively call a single disease, COPD may actually be a hundred different diseases, each with its own unique pattern of symptoms, response to therapy, and disease course.

Although cigarette smoking is the biggest risk factor for COPD, not every smoker develops COPD, and long-term heavy smoking does not always cause the most lung injury. Our research focuses on learning what other factors about an individual may explain the wide variation seen in the onset, severity, and response to treatment of COPD.

Using donated blood samples and lung tissue from hundreds of patients with COPD, the ECRC conducts tests for gene expression, biomarker presence, and bacterial colonization. We also compile radiologic computed tomography (CT) findings and correlate these measures with clinical information about the patients to reclassify COPD into distinct subcategories, or “phenotypes.” Knowing the specific COPD phenotype of a
In This Issue: (continued)

patient may one day help develop an individualized treatment plan to fight the disease, much like the targeted strategies used now for breast cancer.

The centerpiece of the ECRC is the Patient Registry, a group of interested patients with COPD who participate in the collection of information about their disease, including basic screening questions, lung function testing, and blood samples. The Patient Registry has allowed the ECRC to be a national leader in the discovery of new understanding and treatment options for patients with emphysema and COPD.

In this issue, Divay Chandra, MD, MSc, and Matthew Gingo, MD, MS, explore two case studies involving COPD treatment; Jessica Bon, MD, includes an overview of new clinical trials; and Alison Morris, MD, MS, gives an overview on the correlations of HIV-related COPD. Also included are highlights from our 2011 Pittsburgh International Lung Conference, which drew a record number of attendees in October to hear the latest on a range of topics related to personalized medicine for lung disease.

I hope you’ll find this information to be valuable and applicable to your own clinical practice.

With great enthusiasm and respect,

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

Frank Sciurba, MD, FCCP
Director, Emphysema/COPD Research Center
Director, Pulmonary Function Exercise Physiology Laboratory

Correlations of HIV-related COPD

By Alison Morris, MD, MS
Associate Professor of Medicine and Immunology
Division of Pulmonary, Allergy, and Critical Care Medicine

Due to the development of highly active antiretroviral therapy (HAART) to treat the human immunodeficiency virus (HIV), the overall prognosis of patients with HIV has improved dramatically since the first case of acquired immunodeficiency syndrome (AIDS) was reported in 1981. Despite these advances, lung disease remains a leading cause of death and disability in HIV-infected patients. Smoking-related diseases such as emphysema are of particular concern in the HIV-infected population and may actually be increasing despite HIV treatment. We know little about why people with HIV get emphysema at a younger age than people without HIV, and treatment of emphysema in people with HIV may be more difficult than in the general population.

The University of Pittsburgh HIV Lung Research Center (HLRC) was established in 2010 and conducts significant research in HIV-associated lung disease with funded investigators performing studies in human populations and animal models. Our goal is to increase the scientific understanding of HIV-associated lung diseases in order to develop new ways to treat or prevent lung disease in people with HIV. The HLRC is headed by Alison Morris, MD, MS, and Karen Norris, PhD, and includes investigators throughout the University of Pittsburgh community. Scientists are investigating infectious and non-infectious lung complications of HIV. One of the main areas of interest is in HIV-associated emphysema, and we are currently testing people with and without HIV to determine particular risk factors for emphysema in HIV and what causes the disease in people with HIV. We hope that these studies will help us prevent and treat emphysema in people with HIV and lead to a better understanding of emphysema in general.
CASE PRESENTATION:
HIV and Risk for Non-infectious Lung Diseases

By Matthew Gingo, MD, MS
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine

EB is a 56-year-old woman with a history of human immunodeficiency virus (HIV) infection that is well-controlled on treatment with efavirenz-emtricitabin-tenofovir (ATRIPLA®) 600-200-300 mg oral tablets. She has a history of AIDS with Pneumocystis pneumonia (PCP) and thrush in the past, but her serum HIV RNA level (viral load) has been undetectable for > 5 years and CD4 count has been stable in the 900s. EB has a history of intravenous drug and cocaine use and Hepatitis C. She has smoked < 1/2 pack per day of cigarettes for 20 years. Her pulmonary function tests show moderate obstruction with a post bronchodilator ratio of 0.43 and a FEV1 53% of predicted. Her DLCO is 40% of predicted and a chest CT scan shows severe emphysema, more pronounced in both upper lobes (Figure 1).

EB is an example of a patient commonly seen in general medical clinics during the present era of effective antiretroviral therapy (ART) for HIV infection. Even while HIV infection is controlled with effective ART, HIV patients are at increased risk for non-infectious lung diseases such as chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and lung cancer [1-6]. We have found in a sample of subjects from the Pittsburgh AIDS Center for Treatment at the University of Pittsburgh that respiratory symptoms were present in almost two-thirds (63.5%) of the HIV-infected participants [5]. The most common symptoms were dyspnea (43.7%) and having a usual cough (37.1%). Fewer complained of more severe symptoms, such as shortness of breath at rest (6.6%) or coughing more than four times a day on at least four days a week (7.2%). We also found that 71% had some pulmonary function abnormality, with diffusion impairment (DLCO < 80% predicted) being the most common pulmonary function phenotype in 64.1% of participants (Figure 2). While more common in smokers, diffusion impairment was still present in 47.5% of never smokers. Twenty-one percent of participants had irreversible airway obstruction based on a post-bronchodilator FEV1/FVC ratio less than 0.70, and a response to bronchodilator was found in 8.4% of participants. This study showed that respiratory symptoms and pulmonary function abnormalities are quite common in HIV-infected individuals during the current era of effective ART, not unlike Pre-ART [3, 6, 7].

While there may be several factors contributing to this phenomenon, we have found that ART and colonization with Pneumocystis (Pc) are associated with worse airflow obstruction independent of smoking [5, 8, 9]. We hypothesize that low levels of inflammation related to immune reconstitution and colonization of the airways by microbes may play a role in the progression of emphysema and COPD in the HIV-population. We have ongoing studies at the University of Pittsburgh to elucidate the pathogenic roles of antiretroviral medication and the microbiome of the lung in the development of airway obstruction, emphysema, and pulmonary hypertension in the HIV-infected population.

Figure 1. Chest CT scan of EB demonstrating severe emphysema.

Figure 2. Pulmonary function abnormalities in an HIV-infected cohort of all participants (All), those who have ever smoked (Ever smokers), and those who have never smoked (Never smokers). Whiskers represent the 95% confidence interval. BD = bronchodilator; DLCO = diffusing capacity for carbon monoxide.

Lung volume reduction surgery (LVRS), smoking cessation, and supplemental oxygen are the only interventions known to improve survival in patients with emphysema. The UPMC Emphysema/COPD Research Center (ECRC) (www.dept-med.pitt.edu/paccm/ebli.html) was a key research center for the National Emphysema Treatment Trial (NETT), the first and most definitive clinical trial on the safety and effectiveness of LVRS. Having evaluated hundreds of patients for LVRS over the last 15 years with our thoracic surgery colleagues, the physicians at the ECRC are very proficient in the physiologic, radiographic, and functional assessment of patients with COPD so that those patients most likely to benefit from the procedure undergo surgery.

The potential benefits from LVRS in an appropriately selected patient can be summarized by the following example: In 2007, a 63-year-old woman was referred for further management of her debilitating COPD. Despite being on treatment with a comprehensive medication regimen that included fluticasone/salmeterol, tiotropium, and supplemental oxygen, she was only able to climb two to three steps before developing significant dyspnea, and had experienced four exacerbations in the preceding year. Pre-operative physiologic testing (Table 1) and radiographic studies revealed upper lobe predominant emphysema and low exercise capacity, which placed the patient in a favorable prognostic category for improved survival and quality of life with LVRS.

She proceeded with LVRS and 40% of her left and 50% of her right lung volume were surgically resected. Her post-operative course was without complications. She was extubated within two days and discharged home 12 days after surgery. During the two years after surgery she has not required supplemental oxygen, has not had any exacerbations, and has been able to exert herself fully. These improvements also are evident in her physiological parameters (Table 1).

Recent research performed by our group based on NETT data has revealed that lung perfusion measured by perfusion scintigraphy, in addition to the distribution of emphysema and exercise capacity, can identify patients who can experience a 44% reduction in mortality along with clinically significant improvements in exercise capacity and quality of life with LVRS.

For patients who are not found to be suitable or are not interested in LVRS, the ECRC offers a wide variety of innovative new treatments as part of our research studies. Frank Sciurba, MD, FCCP, director of the ECRC, is currently the principal investigator of five NIH-sponsored contracts/grants related to COPD or phenotypic characterization of lung disease, including the NIH Specialized Center in Clinically Oriented Research in COPD (SCCOR) award.

Some recent studies for patients with COPD at the ECRC include:

- A trial evaluating endobronchial valves for Emphysema Palliation (VENT).
- A trial evaluating the effectiveness of statin therapy on reducing the number and/or severity of COPD exacerbations (STATCOPE).
- A trial evaluating the impact of long-acting inhaled anticholinergics on exercise in the early stages of COPD (Tiotropium Exercise Study).
- A trial evaluating the efficacy and safety of long-term oxygen treatment for patients with COPD (LOTT).
- A trial evaluating the efficacy of inhaled cyclosporine for modifying the immune response and possibly slowing disease progression and improving quality of life.

For more details about these trials, please see page 5.

**CASE PRESENTATION:**
Lung Volume Reduction Surgery and the Emphysema/COPD Research Center

By Divay Chandra, MD, MSc
Fellow
Division of Pulmonary, Allergy, and Critical Care Medicine

Lung volume reduction surgery (LVRS), smoking cessation, and supplemental oxygen are the only interventions known to improve survival in patients with emphysema. The UPMC Emphysema/COPD Research Center (ECRC) was a key research center for the National Emphysema Treatment Trial (NETT), the first and most definitive clinical trial on the safety and effectiveness of LVRS. Having evaluated hundreds of patients for LVRS over the last 15 years with our thoracic surgery colleagues, the physicians at the ECRC are very proficient in the physiologic, radiographic, and functional assessment of patients with COPD so that those patients most likely to benefit from the procedure undergo surgery.

The potential benefits from LVRS in an appropriately selected patient can be summarized by the following example: In 2007, a 63-year-old woman was referred for further management of her debilitating COPD. Despite being on treatment with a comprehensive medication regimen that included fluticasone/salmeterol, tiotropium, and supplemental oxygen, she was only able to climb two to three steps before developing significant dyspnea, and had experienced four exacerbations in the preceding year. Pre-operative physiologic testing (Table 1) and radiographic studies revealed upper lobe predominant emphysema and low exercise capacity, which placed the patient in a favorable prognostic category for improved survival and quality of life with LVRS.

She proceeded with LVRS and 40% of her left and 50% of her right lung volume were surgically resected. Her post-operative course was without complications. She was extubated within two days and discharged home 12 days after surgery. During the two years after surgery she has not required supplemental oxygen, has not had any exacerbations, and has been able to exert herself fully. These improvements also are evident in her physiological parameters (Table 1).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BEFORE LVRS</th>
<th>6 MONTHS AFTER LVRS</th>
<th>2 YEARS AFTER LVRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, Liters (% predicted)</td>
<td>0.53 (31%)</td>
<td>1.27 (74%)</td>
<td>1.30 (78%)</td>
</tr>
<tr>
<td>FVC, Liters (% predicted)</td>
<td>1.65 (69%)</td>
<td>2.61 (109%)</td>
<td>3.13 (133%)</td>
</tr>
<tr>
<td>RV, Liters (% predicted)</td>
<td>4.86 (331%)</td>
<td>2.75 (180%)</td>
<td>1.29 (87%)</td>
</tr>
<tr>
<td>TLC, Liters (% predicted)</td>
<td>6.61 (171%)</td>
<td>5.40 (140%)</td>
<td>4.41 (115%)</td>
</tr>
<tr>
<td>Dlco, ml/min/mmHg (% predicted)</td>
<td>7.5 (51%)</td>
<td>9.5 (59%)</td>
<td>10.1 (59%)</td>
</tr>
<tr>
<td>MVV, Liters/min (% predicted)</td>
<td>22 (25%)</td>
<td>51 (57%)</td>
<td>51 (58%)</td>
</tr>
</tbody>
</table>

*Measured 13 months after LVRS*
Current Studies at the ECRC

By Jessica Bon, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine

The Emphysema/COPD Research Center is currently recruiting for several ongoing studies.

The Long-Term Oxygen Treatment Trial (LOTT) is a National Institutes of Health-funded multi-center study for people who have COPD, chronic bronchitis, or emphysema. The goal of the LOTT study is to determine whether treatment with supplemental oxygen results in improved survival and improved quality of life in patients who have moderately low oxygen saturations at rest or during exercise, but who do not meet criteria for supplemental oxygen. Patients who are prescribed supplemental oxygen for exercise and/or sleep also are invited to participate. Participants will be randomly assigned to either supplemental oxygen or to no supplemental oxygen. Participation could last from one to four years with one to two initial study visits, annual clinic visits, and periodic follow-up by telephone and mail.

The STATCOPE Study is another National Institutes of Health-supported study designed to determine whether taking a daily dose of a simvastatin is effective in reducing the number and/or severity of COPD exacerbations. The ECRC is currently enrolling individuals between the ages of 40 and 80 who are smokers or ex-smokers with at least a 10 pack-year smoking history, have been diagnosed with moderate or severe COPD, have experienced exacerbations of their condition, and are not currently taking any statin medications.

The Cyclosporine Study is designed to evaluate the safety and effectiveness of oral cyclosporine in altering the immune system in individuals with COPD. Recent studies have suggested that the immune system may play a significant role in the progression of COPD. Therefore, immunosuppressive medications, such as cyclosporine, may alter the natural disease process. The ECRC is currently seeking individuals between the ages of 45 and 80 who have a confirmed diagnosis of COPD, willingness to participate in all portions of the protocols including serial bronchoscopy, and who meet all other study requirements.

The GSK Arterial Stiffness/COPD Study is designed to test the effect of fluticasone furoate (an inhaled corticosteroid) and vilanterol (an inhaled bronchodilator) on arterial stiffness in patients with COPD. Arterial stiffness is tested non-invasively with a tonometer that characterizes the shape of the pulse, which can then be analyzed to determine arterial stiffness. Individuals over the age of 40 diagnosed with COPD and on a stable medication regimen may be eligible for this study.

Finally, the centerpiece of the ECRC is the Patient Registry, a group of interested patients with COPD that wish to be notified of new trials for which they may qualify. Registry patients participate in the collection of information about their disease, including basic screening questions, lung function testing, and a blood sample. Registry participants have helped the ECRC to be a national leader in the discovery of new understanding and treatment options for patients with emphysema and COPD. We always are seeking individuals with COPD interested in enrolling in our Patient Registry.

If you are interested in learning more about a study, please contact the ECRC at 1-866-948-COPD (2673).
2011 Lung Conference Recap

In a year that included the public presentation of exciting clinical trial results of ivacaftor 1, the first potential drug to target the underlying cause of cystic fibrosis among patients with the G551D-CFTR mutation, it is fitting that the focus of the 10th annual Pittsburgh International Lung Conference was on the Personalized Medicine of Lung Disease. In October 36 distinguished speakers and more than 350 participants met in Pittsburgh to engage in thought-provoking discussions ranging from bioinformatics to genomics, proteomics and translational applications. In addition to outstanding platform presentations and expert panel discussions, there were 55 world-class poster presentations that sparked lively debates among participants.

The 2011 conference opened with a discussion of Future Directions in Lung Research by James P. Kiley, PhD, director of the Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH. The morning’s scientific sessions included state-of-the-art talks focused on COPD and asthma, followed by a featured lunch presentation on Personalized Medicine and Health Care Reform by Steven D. Shapiro, MD, senior vice president and chief medical and scientific officer, UPMC. Afternoon sessions included a focus on Personalizing Acute Lung Injury and an enlightening “bench-to-bedside” panel discussion with representatives from industry and academia. After a dynamic scientific poster session and reception, participants reconvened at the Heinz History Center to bring day one of the conference to a close over a banquet dinner featuring an outstanding presentation by William A. Gahl, MD, PhD, summarizing some of the groundbreaking work done by the NIH Undiagnosed Diseases Program under his directorship.

The momentum and enthusiasm continued on the second and final day of the conference, which opened with a session titled “Information: The Key to Personalized Medicine,” which comprised instructive and highly relevant presentations by leading bioinformatics experts. The day continued with another exciting session titled “Discovering the Gene is Only the Beginning: Lessons from Monogenic Diseases.” Jacob I. Sznajder, MD, chief, Division of Medicine-Pulmonary, Northwestern University Feinberg School of Medicine, closed the morning with a featured lunch presentation titled “From Protein Degradation to Personalized Medicine.” Afternoon sessions focused on Interstitial Lung Disease, Pulmonary Hypertension, and Sleep Medicine. The conference drew to a close with a Conference Summary and Awards Ceremony led by John J. Reilly Jr., MD, the Jack D. Myers Professor and chair of the University of Pittsburgh Department of Medicine.

Enthusiasm and attendance were strong from start to finish, with many conference participants commenting that they gained knowledge that was immediately applicable to their daily practice of the prevention, diagnosis, and treatment of lung disease. Co-chairs Mark T. Gladwin, MD, and Naftali Kaminski, MD, envisioned a conference that would extend beyond the theoretical relevance of cutting-edge scientific discoveries and mere promises of future translational applications. Clearly, the 2011 Pittsburgh International Lung Conference accomplished this goal.

More on the conference is available through these resources:

MEET THE EMPHYSEMA/COPD RESEARCH CENTER TEAM

Frank Sciurba, MD, FCCP
Director, Emphysema/COPD Research Center
Director, Pulmonary Function Exercise Physiology Laboratory
E-mail: sciurbafc@upmc.edu

Khaled Fernainy, MD
E-mail: fernainyke@upmc.edu

Jessica Bon, MD
E-mail: bonjm@upmc.edu

John Reilly, MD
Chair of Medicine
E-mail: reillyj@pitt.edu

Steven D. Shapiro, MD
Chief Medical and Scientific Officer
E-mail: sds33@pitt.edu

The Division of Pulmonary, Allergy, and Critical Care Medicine at UPMC
Pittsburgh, Pennsylvania

Comprehensive Lung Center
3601 Fifth Ave., Fourth Floor
Pittsburgh, PA 15213
T: 412-648-6161
F: 412-648-6869

Mark Gladwin, MD
Professor of Medicine
Chief, Division of PACCM

EDITORS
Matthew Woodske, MD
Assistant Professor
Division of PACCM
woodskeme@upmc.edu

Breann Fiorillo
fiorillobm@upmc.edu

Theresa Dobransky
dobranskyta@upmc.edu

ADDRESS CORRESPONDENCE TO:
Theresa Dobransky, Editor
3459 Fifth Ave.
MUH 628NW
Pittsburgh, PA 15213

For additional information concerning Respiratory Reader or requests for additional newsletter copies, contact Theresa Dobransky at dobranskyta@upmc.edu or call 412-624-8856.

UPMC is a $10 billion global health enterprise with more than 55,000 employees headquartered in Pittsburgh, Pa., and is transforming health care by integrating more than 20 hospitals, 400 doctors’ offices and outpatient sites, a health insurance services division, and international and commercial services. Affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC is redefining health care by using innovative science, technology, and medicine to invent new models of accountable, cost-efficient, and patient-centered care. For more information on how UPMC is taking medicine from where it is to where it needs to be, go to UPMC.com.

To learn more about how UPMC is transforming pulmonary, allergy, and critical care medicine, go to UPMCPhysicianResources.com/Pulmonology