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SHERRY BOSCHERT/IMNG MEDICAL MEDIA

Preparing the hospital and protocols is as important as technical expertise in catheter-directed thrombolysis, Dr. Jeffrey Wang said.

Catheter-Directed Tx in The Community Setting

BY SHERRY BOSCHERT
Elsevier Global Medical News

Few, if any, specialists are aggressively treating massive or submassive pulmonary embolism with catheter-directed thrombolytic therapy at community hospitals, but it is feasible and can have good outcomes with proper planning and preparation, according to Dr. Jeffrey Wang.

Catheter-directed thrombolytic therapy for massive or submassive pulmonary embolism (PE) can shorten stays in the ICU and the hospital, reduce or eliminate the need for home oxygen therapy, and help restore right heart function, he said. However, catheter-directed interventions for these patients is rare outside of academic or tertiary-care settings, probably because of a lack of randomized trials, little retrospective data, and lack of expertise, he said.

For physicians considering this treatment at their own community hospitals, Dr. Wang emphasized that preparing the hospital and protocols is as important as technical expertise in doing the procedure. The fluoroscopy suite must be available on an emergency basis, for example.

"In our institution, we use the same protocols for call-in and transport to the cath lab as for ST-elevation myocardial infarction, which allows us to get the patient up and into the fluoroscopy suite within 30 minutes," said Dr. Wang of Shady Grove Adventist Hospital, Rockville, Md.

Before doing his first case, he made sure that protocols were in place in the emergency department, in the ICU, and with the hospitalist team for the early detection of deep vein thrombosis and PE, notification of the appropriate staff, and posttreatment care of patients.

Systemic anticoagulation has been the mainstay of PE treatment, but the American Heart Association and the American College of Chest Physicians have recommended more aggressive therapy for massive and submassive PEs, Dr. Wang said. Up to 60% of patients with massive

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Desensitization Restores Aspirin's Benefit in AERD

Process can be done on outpatient basis.

BY NEIL OSTERWEIL
Elsevier Global Medical News

ORLANDO – Aspirin sensitivity can be a real headache for patients and clinicians, but a safe and effective aspirin desensitization protocol can bring the analgesic and anti-inflammatory benefits of aspirin therapy to patients with aspirin-exacerbated respiratory disease, reported a clinician at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Patients with AERD who undergo aspirin desensitization have fewer bouts of sinusitis, show improvement in both asthma symptoms and sense of smell, and use less corticosteroid, compared with patients who don't undergo desensitization, said Dr. Katharine M. Woessner, who is program director in the division of allergy, asthma, and immunology at the Scripps Clinic in San Diego.

Aspirin desensitization also blunts the response to other NSAIDs like ibuprofen and naproxen, which – like aspirin – inhibit the cyclo-oxygenase-1 (COX-1) enzyme, Dr. Woessner said. Aspirin and other NSAIDs induce rhinitis and asthma attacks in patients with AERD, and the disease is progressive even when patients are careful to avoid all NSAIDs.

Only 3 of 1,400 consecutive patients with AERD that was treated with aspirin desensitization at Scripps experienced systemic reactions, and all of those responded to a single dose of intramuscular epinephrine, she said.

"I don't know why aspirin desensitization works, but we clearly have a therapy that's easy to use and is quite effective in managing these patients,"

See **Aspirin** • *page 4*

INSIDE

NCCN: Screen High-Risk Smokers

BY DIANA MAHONEY
Elsevier Global Medical News

The benefits of routine lung cancer screening in high-risk individuals outweigh the potential risks, according to members of a National Comprehensive Cancer Network guidelines panel that recommended low-dose helical CT screening of two high-risk groups.

Mary E. Reid, Ph.D., of the Roswell Park Cancer Institute in Buffalo, N.Y., acknowledged the burdens – in particular, the cost and requisite resource utilization – associated with following all high-risk patients who screen positive. But, she said, "the evidence [in favor of] the recommendations is really strong and supports their implementation."

Lung cancer, she noted, is the only one of the top four deadliest cancers (lung, prostate, breast, and colorectal) that is not currently subject to routine screening.

Dr. Reid and her colleagues on the National Comprehensive Cancer Network (NCCN) Guidelines Panel for Lung

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Think Gender, Chronic Bronchitis in COPD

BY PATRICE WENDLING
Elsevier Global Medical News

KEYSTONE, COLO. – Chronic bronchitis and gender might provide more clinically meaningful clues to phenotyping patients with chronic obstructive pulmonary disease than does lung function, recent findings from the COPDGene study suggest.

"There are a lot of important features of COPD that we don't capture by FEV_1, and we need additional clinical features and radiographic information so we can tailor our therapies even more in the future," COPDGene investigator Dr. Barry J. Make, FCCP, said at a meeting on allergy and respiratory diseases.

Researchers with the ongoing COPD genetic epidemiology study used the ATS (American Thoracic Society) questionnaire to identify chronic bronchitis in 1,061 patients with GOLD stage 2-4 COPD. In all, 290 patients had chronic bronchitis, defined as cough and sputum for at least 3 months/year for at least 2 consecutive years, and 771 did not have chronic bronchitis.

The researchers found that chronic bronchitis is a predictor of future COPD exacerbations, said Dr. Make, codirector of the COPD program and medical director of respiratory care services at Denver's National Jewish Health, which sponsored the meeting. The chronic bronchitis–positive group had 1.21 exacerbations/patient per year, compared with 0.63 exacerbations/patient per year in the chronic bronchitis–negative group (*P* less than .027). In addition, more patients in the chronic bronchitis–positive group reported severe exacerbations (26.6% vs. 20%; $P = .024$).

"We're concerned about exacerbations, because if you're hospitalized with an exacerbation of COPD, your mortality within the first year after you get out of the hospital is 20%," he said.

COPD patients with chronic bronchitis were younger, smoked more, were more often current smokers, and had more wheezing and nocturnal awakenings caused by cough and dyspnea. Dr. Make pointed out that the ATS questionnaire is validated to check for cough and sputum, but also emphasized the importance of using CT in assessing patients with COPD.

Notably, patients who have chronic bronchitis have thicker airways on chest CT, compared with the chronic bronchitis–negative group, as indicated by a higher mean segmental wall area percentage (63.2% vs. 62.6%; $P = .013$). Their percent gas trapping and lung emphysema were similar (Chest 2011;140:626-33).

A second COPDGene study in 1,002 COPD patients reported that each 1-mm increase in bronchial wall thickness on quantitative CT is linked with a 1.84-fold increase in annual COPD exacerbations after multivariate analysis that adjusted for lung function, Dr. Make said. The analysis also found that for patients with 35% or greater total emphysema, each 5% increase in emphysema was linked with a 1.18-fold increase in annual exacerbation rate (Radiology 2011;261:274-82).

Thus, COPD patients with chronic bronchitis and emphysema have more exacerbations, and "from CT exam, we can predict a patient's future exacerbations," he said.

Dr. Make pointed out that a history of chronic bronchitis and at least one COPD exacerbation requiring systemic corticosteroids and/or hospitalization were among the inclusion criteria for two pivotal trials that led to the 2011 approval of the phosphodiesterase-4 inhibitor roflumilast (Daliresp). Pooled data from the multicenter trials demonstrated a significant 17% reduction with roflumilast in the rate of moderate or severe exacerbations per patient per year among adult outpatients with COPD (Lancet 2009;374:685-94).

Gender Differences

Women with COPD are known to have more exacerbations than men, to have lower lung function than men with the same cigarette exposure, and to have more symptoms than men with the same lung function. In addition, more women die of COPD, compared with men. Yet, data are limited regarding gender differences in lung anatomy that might explain this troubling paradox, at least in part. Dr. Make highlighted a recent study that identified gender differences in airway dimensions in 1,021 male and 1,026 female smokers in the COPDGene cohort (COPD 2011;8:285-92).

Multidetector CT scans of the chest revealed that in all airways measured, women smokers had higher wall area percentage but smaller luminal area, internal diameter, and airway wall thickness than did male smokers. Gender remained one of the most significant predictors for these differences on multivariate analysis, even after researchers adjusted for age, body size, and other confounders.

Dr. Make reported ties to several pharmaceutical companies and the National Heart, Lung, and Blood Institute. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: We know that lung function doesn't explain all that is COPD, and this work (whose earlier findings were published in *Chest*) highlights the importance of other factors such as chronic bronchitis and gender in COPD. While it is surprising that less than 28% of COPD study subjects had questionnaire-based chronic bronchitis, its presence was associated with more frequent exacerbations. The time has come to both acknowledge and accept that many factors and characteristics contribute to disease progression and outcomes in COPD.

IN THIS ISSUE

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Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of CHEST PHYSICIAN.

CHEST PHYSICIAN

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For PAH (WHO Group 1) patients on oral monotherapy

TYVASO: the ONLY inhaled prostacyclin analogue approved for 4x-daily dosing[1]

Short treatment sessions: just 2 to 3 minutes each[2]

ONLY inhaled prostacyclin analogue approved as an add-on to oral PAH monotherapy[1]

- 52% of patients improved 6MWD by greater than 20 m[3]
- Improvement in 6MWD at peak (20 m) and trough (14 m) exposure[3]

Dosing regimen fits into patients' schedules

- Short treatment sessions: just 2 to 3 minutes, 4x daily[2]
- Set up once daily[1,2]
  - —One plastic ampule per day—no need to replace ampule for each treatment session[1]
  - —About 5 minutes a day for device preparation—once in the morning, and the device is ready to go all day[2]
- Treatment timing can be adjusted for planned activities[1]

Adverse events

- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope[1]

STUDY DESIGN: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.[3]

INDICATION

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

IMPORTANT SAFETY INFORMATION

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)
- Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. WHO=World Health Organization.

References: 1. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011. **2.** Tyvaso [patient package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011. **3.** McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922.

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TYVASO® (treprostinil) INHALATION SOLUTION

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Regaining Benefits of Analgesia

Aspirin • *from page 1*

Dr. Woessner said. AERD usually begins in patients in their 30s or 40s who have a prior history of tolerance to aspirin and other NSAIDs. It is more than twice as likely to occur in women, and tends to be more severe in women than in men. Patients develop chronic congestion, rhinitis, anosmia, and nasal polyps, often followed by asthma 1-5 years after the onset of rhinitis.

The disease is characterized by chronic eosinophilic rhinosinusitis and nasal polyposis that are initially intermittent but evolve into chronic, hyperplasic eosinophilic sinusitis that often requires surgical intervention, Dr. Woessner said.

The asthma that develops in patients with AERD is persistent, usually moderate to severe, and related to the severity of sinus disease. However, "asthma is not necessarily a prerequisite to make a diagnosis of aspirin-exacerbated respiratory disease," she noted.

Aspirin Challenge

The clinical standard for AERD diagnosis is an oral aspirin challenge. Patients typically can experience a 20% or greater decline in FEV_1 (forced expiratory volume in 1 second) and a naso-ocular reaction, but purely upper airway or lower airway reactions can also occur. Patients may also have a partial asthma reaction, with a change in FEV_1 from baseline of –15% to –20% and a naso-ocular reaction or laryngospasm. Patients are considered to be negative for AERD if they have no reactions following a 325-mg oral aspirin challenge.

In those who test positive, treatment consists of avoiding all COX-1–inhibiting NSAIDs. Highly selective COX-2 inhibitors such as celecoxib (Celebrex) are generally well tolerated in patients with AERD, Dr. Woesnner said, noting that more than 200 AERD-proven patients at Scripps who were challenged with a highly selective COX-2 inhibitor had no reaction. However, cross-reactivity is possible with higher doses of less-selective COX-2 inhibitors such as nimesulide (Sulide) or meloxicam (Mobic). Acetaminophen at doses up to 1,000 mg are also typically well tolerated in these patients.

"There are several drugs that don't cross-react with aspirin in patients with AERD. The problem is that they're not very good analgesics, so if we need something that's analgesic or anti-inflammatory, patients are not going to get much benefit from these medications," Dr. Woessner said.

Outpatient Precautions

Aspirin challenge and desensitization in the outpatient setting can be safely performed with a few caveats. The patient should have stable asthma within 10% of the best prior value and an FEV_1 of at least 60%-80% of predicted, or an output of at least 1.5 L. The patient should be on inhaled steroids and a long-acting beta-agonist, and 2-4 weeks before desensitization should be started on montelukast or another leukotriene modifier.

The advent of leukotriene inhibitors has made aspirin desensitization a routine outpatient procedure, session moderator Dr. Mariana C. Castells noted in an interview.

"We used to do aspirin desensitization in the intensive care unit, just because the reactions were scary and we didn't know how to control them. In the last 10 years, since we started to use montelukast [Singulair] and Zyflo [zileuton], less than 1% have been done in an intensive care unit," said Dr. Castells of the division of rheumatology, immunology, and allergy at Brigham and Women's Hospital in Boston.

Patients are asked to not use antihistamines for 72 hours before the procedure so that their naso-ocular responses can be observed. Patients with nasal polyps may require debulking surgery prior to desensitization.

"We had recommended in the past that intravenous access be available, but we have data now that it may not be necessary," Dr. Woessner said.

On day 1 of sensitization, patients take 20-40 mg of aspirin at 8 a.m., 40-60 mg at 11 a.m., and 60-100 mg at 2 p.m. On day 2, the respective doses at the same times of day are 100-160 mg, 160-325 mg, and 325 mg.

During desensitization, FEV_1 should be measured every hour, and should be at least 1.5 L and greater than 60% of predicted. When a patient has a reaction and that reaction is resolved, the provoking dose should be repeated, and if

Continued on following page

Airway Abnormalities May Represent Preclinical RA

BY BRUCE JANCIN
Elsevier Global Medical News

SNOWMASS, COLO. – Where does rheumatoid arthritis hang out in the body preclinically during the years following autoantibody formation but before symptomatic joint involvement?

Increasing evidence suggests that RA is smoldering in the lungs during this preclinical stage, which can last a decade or more. Indeed, bronchiole-associated lymphoid tissue may actually be the site where tolerance is broken and RA-related autoimmunity and systemic inflammation are generated, according to Dr. William F.C. Rigby, professor of medicine and professor of microbiology and immunology at Dartmouth Medical School, Hanover, N.H.

He credited the discovery of the existence of a lengthy preclinical seropositive phase of RA to landmark studies involving U.S. military personnel with centrally stored blood samples that were available for many years prior to their being diagnosed with RA (Ann. Rheum. Dis. 2008; 67:801-7). The existence of this years-long preclinical lag time has since been confirmed in multiple other populations.

Recently, investigators at the University of Colorado at Denver, Aurora, identified the lung as an early site of autoimmune-related injury in subjects with what is being called preclinical seropositive RA (Arthritis Rheum. 2011 Dec. 19 [doi:10.1002/art.34344]).

"This is a great paper, profound in its implications," Dr. Rigby commented at a symposium sponsored by the American College of Rheumatology.

By conducting mass screenings at an annual Colorado health fair, the investigators identified a cohort of 45 subjects with preclinical RA (defined by elevated anti–cyclic citrullinated peptide antibodies and/or two or more rheumatoid factor isotypes, along with no evidence of arthritis on a 68-joint examination). Earlier work with the Armed Forces cohort had established that this serologic profile is 96% specific for RA.

All 45 subjects underwent chest CT with blinded scan readings. So did 16 seronegative healthy controls matched for age, sex, and smoking status, as well as 12 patients with early RA diagnosed less than 1 year before.

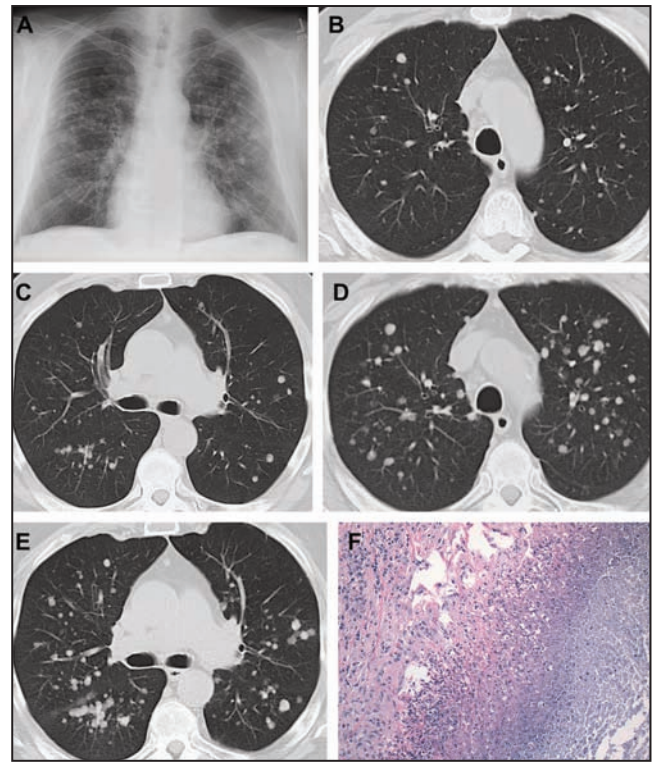
The prevalence of airways disease on CT (air trapping, bronchial wall thickening, bronchiectasis, and/or centrilobular opacities) was 77% in the autoantibody-positive preclinical RA group, compared with 31% of controls. Moreover, none of the seropositive preclinical RA subjects with CT lung abnormalities had any evidence of synovitis of their joints on MRI, indicating that RA isn't smoldering preclinically in their joints for a long time prior to the time they show up in a rheumatologist's office with joint symptoms. The prevalence of CT airways changes in the early RA group was similar to that in the preclinical seropositive group.

Of note, none of the subjects with preclinical RA had CT evidence of interstitial lung disease; it was all airways disease, Dr. Rigby observed.

The lung is quite plausible as the site where tolerance is broken (that is, autoantibodies against self-proteins such as cyclic citrullinated peptides are first formed), in light of the fact that smoking is a well-established environmental risk factor for RA, associated with a greater than fivefold increased risk of the rheumatologic disease in epidemiologic studies. Infectious respiratory illness could also hypothetically serve as a trigger for the breaking of tolerance, the rheumatologist said.

Some research groups are homing in on the gut or periodontal colonization by *Porphyromonas gingivalis* as possible key sites where tolerance is broken in individuals who will years later be diagnosed with RA. At this time, however, Dr. Rigby considers the evidence for the lung as the major player to be further along and more persuasive.

He reported having no financial conflicts. ■



In a 66-year-old man with RA, chest radiograph (A) shows multiple lung nodules bilaterally. CT images of the upper thorax (B) and midthorax (C) show bilateral lung nodules with a random distribution. CT scans 1 year later (D, E) show an increase in number and size of lung nodules. Surgical lung biopsy revealed necrobiotic (rheumatoid) nodules (F).

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: Detailed understanding of immunologic "self vs. nonself" remains somewhat of an enigma. This article presents evidence suggesting breakdown in the lungs with a loss of immune tolerance may predispose to the development of RA. Patients with seropositive, preclinical RA were found to have a significantly higher likelihood of airways disease noted on CT scan. These findings have important implications for possible early treatment of RA prior to joint destruction, along with furthering our understanding of autoantibody production and the potential role of the lung.

Continued from previous page

there is no reaction, the escalating doses can be continued every 3 hours as scheduled. Patients are considered to be densensitized or aspirin tolerant if they can take a 325-mg dose with no reaction. The patient should be instructed to start on 650 mg aspirin that night as the first daily dose, and to continue with up to 650 mg twice daily. About half of all patients can decrease to 325 mg b.i.d. at 1-6 months after the densensitization protocol is completed.

Combining a nasal ketorolac challenge with the oral aspirin challenge can make the desensitization even safer, Dr. Woessner said. The patient is given ketorolac spray at increasing doses every half-hour over 2 hours, followed 1 hour after the last spray with 60 mg aspirin in two doses 1.5 hours apart. The patient is discharged and returns the next day to receive 150 mg aspirin, followed 3 hours later by 325 mg.

No funding source was reported. Dr. Woessner disclosed that she is on the speakers bureaus of Merck and Teva, and has been a speaker for GlaxoSmithKline. ■

10 Biomarkers May Aid Lung Cancer Detection

BY DENISE NAPOLI
Elsevier Global Medical News

A panel of 10 serum biomarkers for lung cancer could offer more accurate interpretation of nodules detected on CT, avoiding invasive biopsies and radiographic follow-up.

"CT screening detection of an indeterminate pulmonary nodule, a nonspecific but frequent finding in high-risk subjects with a smoking history, creates a diagnostic dilemma," wrote William L. Bigbee, Ph.D., and colleagues.

"Although the biomarker model we described could not detect every lung cancer, it offers a significant clinical improvement over CT imaging alone. … Also, patients with nodules not identified as cancer by the model would continue to receive follow up clinical monitoring and would be biopsied if the nodules grew in size, which is the current standard of care" (J. Thorac. Oncol. 2012;7:698-708).

Dr. Bigbee of the University of Pittsburgh and his colleagues cite results of the National Lung Screening Trial (NLST), published in June 2011, which showed for the first time that low-dose CT screening of heavy smokers could reduce lung cancer mortality by 20%. But, as the researchers note in the current study, the "vast majority" of positive results in the NLST program turned out to be false after diagnostic evaluation. Moreover, smaller nodules are least likely to be malignant and least likely to be considered for biopsy or surgery.

For the current study, the researchers initially looked at a "training" set of 56 patients with non–small cell lung cancer in the University of Pittsburgh Cancer Institute Georgia Cooper Lung Research Registry. These cases were matched with 56 controls from the Pittsburgh Lung Screening Study (PLuSS), a volunteer cohort at high risk for lung cancer. All controls were known to be cancer free. The authors then analyzed serum samples from both groups for the presence of 70 potential cancer-associated biomarkers.

"Together, these biomarkers incorporate a wide range of host and tumor derived factors that allow a broad analysis of the lung cancer/host interaction, and includes a number of previously described epithelial cell cancer-associated serological markers," wrote the investigators. "The initial goal of this discovery study was to identify the most robust subset of these biomarkers to discriminate lung cancer and matched control samples." Using a rule-learning algorithm, they narrowed the field of potential biomarkers to eight: prolactin, transthyretin, thrombospondin-1, E-selectin, C-C motif chemokine 5, macrophage migration inhibitory factor, plasminogen activator inhibitor 1, and receptor tyrosine-protein kinase erbB-2.

'THE BIOMARKER MODEL WE DESCRIBED ... OFFERS A SIGNIFICANT CLINICAL IMPROVEMENT OVER CT IMAGING ALONE.'

"This rule model distinguished the lung cancer case samples from the control samples in the training set with a sensitivity of 92.9% and specificity of 87.5%," the researchers reported.

Ultimately, two additional biomarkers were added to the panel – cytokeratin fragment 19-9 and serum amyloid A protein – and an additional set of cases and controls, 30 in each cohort, was assessed, in a blinded "verification" set.

In this set, the authors calculated an overall classification performance of 73.3% sensitivity and 93.3% specificity. Only 10 misclassifications occurred among 60 predictions made. Moreover, when looking at accuracy according to patient demographic factors, the researchers found that the 10-biomarker panel was equally good at distinguishing males and females as either cases or controls and that neither current smoking status nor airway obstruction skewed the results.

"Age overall was not a significant factor in misclassification of cases or controls, although two of three cases aged 38-44 [years] were misclassified as controls by the 10-biomarker model," the authors said. "This inaccuracy may result from the absence of younger subjects in the training set that included no cases younger than 46 years at diagnosis and no controls younger than 50 years."

Nor did the presence of nodules visible on CT scan confound the biomarkers' predictive value. "In fact, those PLuSS subjects with a suspicious nodule were more often correctly classified as controls than those with no nodule or a benign nodule," wrote the authors.

They added that all nodules found in controls remained clinically noncancerous at least 3 years after initial detection, with either resolution or no further growth on subsequent CT scans.

Finally, Dr. Bigbee and associates assessed the model's accuracy when confronted with early- vs. late-stage tumors.

"Among stage I/II lung tumors, the 10-biomarker panel misclassified 15% of stage I/II tumors in the verification set, compared to 50% of the stage III/IV tumors, suggesting the model performs well in discriminating early-stage lung cancer," they wrote. "With a specificity of 93.3%, the 10-biomarker model was 89.2% [accurate] in stage I/II disease."

The authors conceded that the biomarker panel presented here would not suffice for general population screening. However, in a clinical context, among high-risk patients, the model "may provide clinical utility in guiding interpretation of screening CT scans, even in tobacco-exposed persons with COPD or emphysema," they wrote. "Formal validation in larger patient cohorts will be needed to confirm these initial findings."

This study was funded by grants from the National Cancer Institute. There were no personal disclosures. ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: This is an intriguing retrospective study of the accuracy of using a panel of 10 serum biomarkers to predict the presence of lung cancer. In this small study, the predictive accuracy was 89.2%, offering tantalizing promise that in the future, this technique might help in the interpretation of suspicious nodules found on screening CT scans. Larger, prospective studies of this technique are warranted to assess the clinical potential of using this expensive panel of serum markers in routine clinical decision making with lung masses.

New NCCN Guidelines

Screen • *from page 1*

Cancer Screening presented the update at the NCCN annual conference. The revised guidelines recommend annual low-dose helical CT screening for the following two groups of high-risk individuals:

► Those aged 55-74 years with a minimum smoking history of 30 pack-years who either are current smokers or quit within the past 15 years.

► Those aged 50 years or older with a minimum smoking history of 20 pack-years plus one additional lung cancer risk factor.

Evidence from the randomized, controlled National Lung Screening Trial (NLST) suggests that early detection via screening reduced lung cancer–specific mortality in the former risk group, which characterizes the NLST patient population. Specifically, 1 in 100 high-risk individuals enrolled in the study screened positive on their first low-dose CT exam, and one life was saved for every 320 high-risk individuals screened over 2 years (three screens) (N. Engl. J. Med. 2011;365:395-409). The NCCN recommendation for this group is category 1, the highest level.

The recommendation for annual screening in the second high-risk group is based on less-robust evidence and a nonuniform consensus of the NCCN panel members, Dr. Reid said. As such, it is a less-emphatic category 2B recommendation.

The NCCN screening recommendations have been deemed by some experts to be premature in the absence of cost-efficacy analysis, particularly because of the high false-positive rates seen in both the CT group (96.4%) and the radiography group (94.5%), as well as the potentially harmful effects of radiation exposure associated with low-dose CT screening.

Despite the favorable outcome of their study, the NLST authors stressed the need for rigorous cost-effectiveness analyses before the crafting of public policy recommendations. "The reductions in lung cancer mortality must be weighed against the harms from positive screening results and overdiagnosis, as well as the costs," they wrote.

In addition to recommending appropriate candidates for routine screening and the proposed frequency of the scans, the new NCCN guidelines outline lung cancer risk factors, address the risks and benefits of screening as well as screening accuracy, and offer an algorithm for the evaluation and follow-up of positive screens.

Specifically, the guidelines recommend the following:

► Basing the frequency of low-dose CT in high-risk patients on the size and status (solid, nonsolid, part-solid, ground-glass, ground-glass opacity) of the nodule on baseline CT.

► Excising all nodules that increase in size or become solid or partly solid during follow-up.

► Considering PET with CT for nodules 8 mm or larger at baseline.

► Performing biopsy or excision of nodules that are suspicious for lung cancer, based on PET with CT findings.

► Reexamining within 1 month solid endobronchial nodules with low-dose CT immediately after vigorous coughing.

► Counseling smokers to quit.

The NCCN is the first professional organization to recommend routine low-dose CT screening for individuals who are considered to be at high risk for lung cancer, according to Dr. Reid. Last summer, the International Association for the Study of Lung Cancer issued a call for physicians to discuss lung cancer screening with patients with a high-risk smoking history.

Dr. Reid disclosed no financial conflicts of interest. Disclosures of the NCCN Guidelines Panel for Lung Cancer Screening are online. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: The NCCN has recommended annual low-dose CT screening for lung cancer in two groups of patients. The first exactly mirrors the entry criteria used in the NLST study. The second group includes those age 50 or older with a greater than 20 pack-year history of smoking along with an additional lung cancer risk factor. Literature support exists for the former but not the latter. The latter recommendation is not evidence based. All hope that a mortality benefit can be shown in the latter group. We just don't know.

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

COPD EXACERBATIONS

are serious events...

Reducing Patient Risk Is Critical

INDICATIONS AND USAGE

DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Please see Important Safety Information and Brief Summary of full Prescribing Information on the following pages and at www.DALIRESP.com.

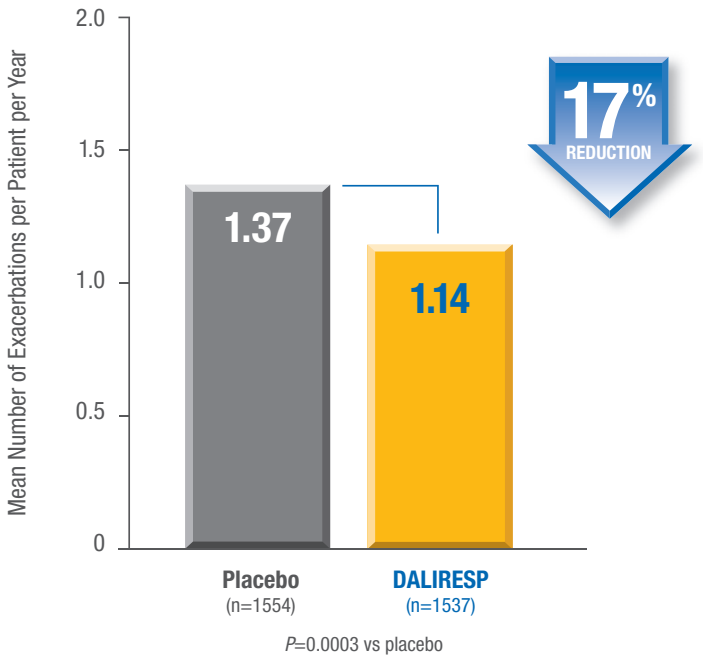
COPD=chronic obstructive pulmonary disease.

Daliresp®
(roflumilast) tablets
500 mcg

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

DALIRESP® is the first and only selective PDE4 inhibitor to reduce the risk of COPD exacerbations[1,2]

REDUCTION IN THE RATE OF MODERATE OR SEVERE EXACERBATIONS[3,4]



Study design: A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs or short-acting anticholinergics were allowed as concomitant treatment. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV_1) were co-primary endpoints. Each study met both co-primary endpoints.

- Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids[1]
- Severe exacerbations were defined as resulting in hospitalization and/or death[1]
- DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm[1]

IMPORTANT SAFETY INFORMATION

Contraindications

DALIRESP is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions

- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.
  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.

References: 1. DALIRESP (roflumilast) Prescribing Information. Forest Pharmaceuticals, Inc. St. Louis, MO. **2.** US Food and Drug Administration. FDA news release. March 1, 2011. http://www.fda.gov/NewsEvents/newsroom/PressAnnouncements/ucm244989.htm. Accessed February 13, 2012. **3.** Data on file. Forest Laboratories, Inc. **4.** Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374:685-694.

In the same studies:

DALIRESP significantly reduced the rate of exacerbations vs placebo in patients using a bronchodilator[1,3]

CONSISTENT EFFECT WITH A CONCOMITANT BRONCHODILATOR[1,3]

DALIRESP with LABAs (Long-acting ß$_2$ Agonists)	✓
DALIRESP with Short-acting Anticholinergics	✓

- The effect with concomitant LABAs or short-acting anticholinergics was similar to that seen in the overall population[1,3]

ONCE-DAILY
ORAL

Tablet shown not actual size.

- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.
- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP.

Adverse Reactions

In clinical trials the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see Brief Summary of full Prescribing Information on the following page and at www.DALIRESP.com.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Daliresp®
(roflumilast) tablets
500 mcg

 84-12000502T 03/12

DALIRESP® (roflumilast) tablets **Rx Only**
Brief Summary of Full Prescribing Information

Initial U.S. Approval: 2011

INDICATIONS AND USAGE
DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS
The use of DALIRESP is contraindicated in the following conditions:

Moderate to severe liver impairment (Child-Pugh B or C) [*see Clinical Pharmacology (12.3) and Use in Special Populations (8.6)*].

WARNINGS AND PRECAUTIONS
Treatment of Acute Bronchospasm
DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events including Suicidality
Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) *[see Adverse Reactions (6.1)]*. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease
Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1)*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (eg. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended. [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2)]*
- Weight Decrease *[see Warnings and Precautions (5.3)]*

Adverse Reactions in Clinical Studies
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP** (**N=**4438) n (%)	**Placebo** (**N=**4192) n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting

Infections and infestations - rhinitis, sinusitis, urinary tract infection,

Musculoskeletal and connective tissue disorders - muscle spasms

Nervous system disorders - tremor

Psychiatric disorders - anxiety, depression

DRUG INTERACTIONS
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [*see Clinical Pharmacology (12.3)*].

Drugs That Induce Cytochrome P450 (CYP) Enzymes
Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3)]*.

Drugs That Inhibit Cytochrome P450 (CYP) Enzymes
The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. *[see Clinical Pharmacology (12.3)]*.

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol
The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses > 2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

Labor and Delivery
DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of > 2 mg/kg/day).

Nursing Mothers
Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use
COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use
Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

Hepatic Impairment
Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Renal Impairment
In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

OVERDOSAGE
Human Experience
No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose
In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

Manufactured by:
Nycomed GmbH.
Production Site Oranienburg
Lehnitzstrasse 70 – 98
16515 Oranienburg
Germany

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

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084-12000414-B-T-RMC17137-SEP11

Please also see full Prescribing Information at www.daliresp.com.

Treating PEs Outside Tertiary Care

Community • *from page 1*

PE die, data suggest, with two-thirds of the deaths occurring in the first hour of embolism formation. Within 30 days of submassive PE formation, 15%-20% of patients die secondary to pulmonary hypertension and cor pulmonale.

Approximately 30% of all 500,000 symptomatic PEs diagnosed each year in the United States lead to death. Even among inpatients who are diagnosed with a PE while in the hospital, the mortality rate is approximately 10%-15%, he said.

Until recently, there was no Food and Drug Administration–approved device for catheter-directed thrombolytic therapy. "There's also not a purpose-built device to help you with these types of procedures," Dr. Wang said.

At the annual meeting of the Southern Association for Vascular Surgery, he described treating nine women and three men who had a total of seven massive and five submassive PEs. Catheter-directed thrombolytic therapy was offered to patients with massive or submassive PE if they were hemodynamically unstable or had right heart dysfunction, elevated troponin levels, or pulmonary artery pressures greater than 70 mm Hg, or if they were not being weaned off intubation for oxygen within 5 days, Dr. Wang said. He excluded patients who were actively bleeding or who were not able to tolerate any systemic anticoagulation – "not even aspirin," he said.

Recent surgery was not a disqualifying factor. "Typically those patients were orthopedic in nature, with a hip or knee replacement," Dr. Wang said. The patient would develop a big PE, and the orthopedist would give him the green light for aggressive treatment.

All procedures were technically successful. One patient developed hemodynamically significant bradycardia, but all were off supplemental oxygen within 24 hours of the procedure, and there were no bleeding events.

One patient died 14 hours after the procedure, most likely due to a paradoxical embolism to the intestine, Dr. Wang said. The 11 surviving patients were discharged to home within 48 hours of the intervention.

His technique includes accessing the internal jugular vein to get to the pulmonary artery, placing a vena cava filter, and giving tissue plasminogen activator as the lytic agent. All patients had a spiral CT scan before going to the catheterization lab, so pulmonary angiography was not routinely performed.

He reserved mechanical (catheter) thrombectomy for some patients with massive thromboembolism. Instead of being guided by angiography, he determined the duration of mechanical thrombectomy by the patient's blood pressure, pulse, and oxygen saturation. "I discontinued mechanical thrombectomy once oxygen saturation was above 95%, they're weaning off their inotropes, and the pulse rate was trending toward normal," he said.

For some patients who developed nonsinus arrhythmias due to the wire manipulations within the heart and pulmonary arteries, he removed the wire device, waited for it to resolve, and continued. A minority of patients whose arrhythmias continued to occur during the intervention received calcium blockade or beta blockade.

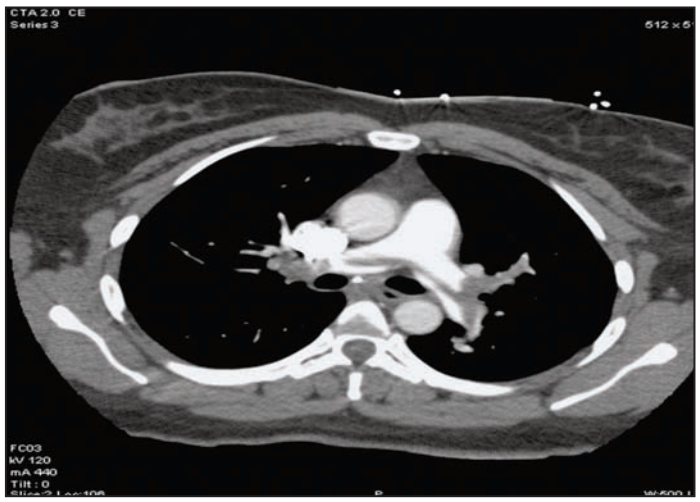
Patients who received mechanical thrombectomy developed dark or bloody urine that resolved within 48 hours with hydration.

Follow-up at 2 weeks assessed general function and access sites, and patients had a repeat echocardiogram at 1 month. If they were doing well functionally and pulmonary hypertension had resolved, Dr. Wang offered to remove the vena cava filter. All but one patient accepted. All were to remain on systemic anticoagulation for 6-12 months, and patients with massive PE underwent hematologic work-ups.

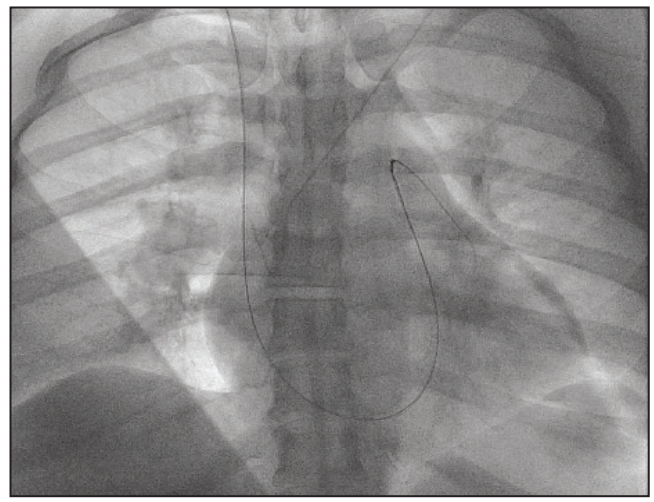
Dr. Wang reported having no financial disclosures. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: The portability and simplicity of today's medical technology have allowed every hospital to perform procedures reserved for top centers in the past. This is of significance especially in small towns as long travel is a risk factor for DVT and PE. However, this approach has to be studied in a randomized, controlled manner for its use to be expanded.



A CT scan shows that this patient needs thrombolysis in both the right and left pulmonary arteries.



Pulmonary angiography shows the catheter in place to deliver the lytic agent.

IMAGES COURTESY DR. JEFFREY Y. WANG

Rivaroxaban Found 'Noninferior' to Standard PE Therapy

BY MARY ANN MOON
Elsevier Global Medical News

Rivaroxaban was noninferior to standard treatment at preventing a recurrence of pulmonary embolism in an international open-label trial reported online in the New England Journal of Medicine and presented simultaneously at the annual meeting of the American College of Cardiology.

Rates of adverse bleeding events with rivaroxaban were similar to those with the more complex standard therapy of enoxaparin plus a vitamin K antagonist, a regimen that requires INR (international normalized ratio) monitoring, said Dr. Harry R. Buller of the department of vascular medicine at the University of Amsterdam and his associates in the EINSTEIN-PE clinical trial.

The study involved 4,832 adults with acute symptomatic pulmonary embolism (PE), with or without deep vein thrombosis (DVT), who were treated at 263 sites in 38 countries in 2007-2011. In all, 2,419 study subjects were randomly assigned to receive oral rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) and 2,413 to receive enoxaparin (1 mg/kg twice daily, which was discontinued when the INR reached 2.0 or greater for 2 consecutive days after at least 5 days of therapy) plus either warfarin or acenocoumarol at a dosage adjusted to maintain an INR of 2.0-3.0.

All study subjects were treated for durations of 3, 6, or 12 months, according to the wishes of their treating physicians and in keeping with current practice. The mean duration of treatment was about 9 months.

In the standard treatment group, the INR was in the therapeutic range 62.7% of the time. The INR was not measured in the rivaroxaban group, but adherence to therapy was high in 94.2% of patients.

The primary efficacy outcome was symptomatic recurrent venous thromboembolism, a composite of fatal and nonfatal PE or DVT. This occurred in 50 patients (2.1%) receiving rivaroxaban and 44 (1.8%) receiving standard therapy, which met the criterion for noninferiority, the investigators said (N. Engl. J. Med. 2012 March 26 [doi:10.1056/NEJMoa1113572]).

During the initial 3-week period of intensive rivaroxaban therapy, the primary efficacy outcome occurred in 18 patients (0.7%) of the rivaroxaban group and in 21 patients (0.9%) in the standard therapy group.

The efficacy results were similar in a per-protocol analysis and in an intention-to-treat analysis.

The primary safety outcome was clinically relevant bleeding, and it occurred in 249 subjects (10.3%) in the rivaroxaban group and in 274 (11.4%) in the standard treatment group. In particular, major bleeding events occurred in 26 patients (1.1%) taking rivaroxaban and 52 (2.2%) taking standard treatment.

During the initial 3-week period of intensive rivaroxaban therapy, bleeding rates were similar between the two study groups. Over the full course of treatment, "there were fewer episodes of intracranial bleeding or bleeding in critical areas in the rivaroxaban group than in the standard therapy group," Dr. Buller and his colleagues said.

With regard to other safety outcomes, the rates of acute coronary events were similar between the two study groups, at 0.6% with rivaroxaban and 0.9% with standard therapy. Abnormal findings on liver function tests were seen in 0.2% of both groups. ■

VITALS

Major Finding: PE, with or without DVT, recurred in 2.1% of patients receiving rivaroxaban and in 1.8% of those taking standard preventive therapy, meeting the prespecified criterion for noninferiority.

Data Source: This was a 4-year, randomized, open-label, noninferiority trial comparing rivaroxaban (2,419 subjects) and standard treatment (2,413 subjects) in 38 countries.

Disclosures: This study was supported by Bayer HealthCare and Janssen Pharmaceuticals. Dr. Buller reported ties to ICTOM/Bayer HealthCare, Sanofi-Aventis, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, and Daiichi Sankyo, and his associates reported ties to numerous industry sources.

Insomnia Responds to Cognitive-Behavorial Approach

BY M. ALEXANDER OTTO
Elsevier Global Medical News

PHOENIX – Reducing bedtime stimulation and, oddly enough, restricting sleep both have powerful, relatively fast effects on insomnia, especially when used in tandem.

Among cognitive-behavioral therapy approaches, they have the best supporting evidence and, "happily, are the easiest to do," said Allison Harvey, Ph.D., director of the University of California, Berkeley, Golden Bear Sleep and Mood Research Clinic.

The goal is to teach insomniacs that their beds are for sleeping, not watching TV, surfing the Internet, eating potato chips, or fretting about not getting enough sleep.

Sleep restriction limits their time in bed to the time they actually sleep. The first step is to discover that ratio by having patients keep a sleep diary for a week or two. Insomniacs are usually about 60% sleep efficient; for every 8 hours in bed, they'll sleep about 5.

TEACH INSOMNIACS THAT THEIR BEDS ARE FOR SLEEPING, NOT WATCHING TV, SURFING THE INTERNET, OR EATING POTATO CHIPS.

The next step is limiting bed time to sleep time. At first, that might cause a bit of sleep deprivation, but that's a good thing because it builds homeostatic pressure to sleep, Dr. Harvey explained at a meeting on sleep medicine held by the American College of Chest Physicians.

The goal is 85% sleep efficiency: 4.25 hours of sleep, for instance, for every 5 hours in bed. As long as patients remain 85% efficient, time in bed can be increased by 15 minutes every 5 or so days. Within about 6 weeks, patients should be getting an efficient 7 or 8 hours of sleep per night.

At first, "we never go less than 5 hours a night" and "make the determination of how low we go dependent on safety issues. So, if someone's a truck driver, we probably wouldn't do this treatment. If someone has bipolar disorder, I would not go below 6½ hours because sleep deprivation can trigger a manic episode." Naps are okay if needed, as long as they are before 3 p.m. and are 30 minutes or less, Dr. Harvey said.

Stimulus control reinforces the bed-sleep connection. If patients aren't asleep within 20 minutes, "don't let them clock watch. [Tell them to] get up and move to another room, and stay up until they are really sleepy," she said.

If they want to read, it shouldn't be something that will keep them up all night. If they want to watch TV, it should be something relaxing, not just channel surfing. If they're anxious, writing in a journal can help.

"I had one patient who said, 'Oh, I can get some housework done.' No. Nothing productive. Other patients say, 'I can get on my computer and do some e-mail.' No. [They need] dim light conditions," Dr. Harvey said.

Flexibility is important. Some patients might want to restrict sleep in the evening, others in the morning. Both are fine. Some patients might worry that 5 hours is too little bedtime, so "start with 7½ – it's better than 8½. Sleep efficiency will pop up a bit, they'll get confidence. They'll come down to 7 hours the next week. Just base it on what makes sense for the person," Dr. Harvey said.

It might take a few weeks for patients to see benefits, so support is important, too. Troubleshoot their routine for problems, and encourage them to continue the program, she said. It's uncertain what benefit sedative hypnotics such as zolpidem (Ambien) would add to the approach, she noted.

Dr. Harvey reported having no relevant financial disclosures. ■

COMMENT

Dr. Vera De Palo, FCCP, comments: Stimulus control, sleep restriction therapy, cognitive therapy, and improved sleep hygiene are important elements of cognitive-behavioral treatment for insomnia.

Several First-Line Drugs Available for Insomnia

BY M. ALEXANDER OTTO
Elsevier Global Medical News

PHOENIX – It's a good idea to remind insomnia patients not to mix benzodiazepine receptor agonists – zaleplon, zolpidem, and eszopiclone – with antihistamines, antinausea drugs such as promethazine, or alcohol.

Mixing the so-called Z-drugs with those or other sedating agents can trigger sleepwalking, sleep driving, or sleep eating, among other problems, in approximately 1 in 1,000 people. Those affected might "get up in the morning and find the kitchen is a mess and all the food is pulled out of the refrigerator. They'll have no memory of it," said Dr. James Parish, FCCP, medical director of the center for sleep medicine at the Mayo Clinic in Scottsdale, Ariz.

When Dr. Parish prescribes a Z-drug, "I warn people about this effect and [that] if this happens, they should stop [the drug] immediately and not use it again," he said.

Otherwise, the Z-drugs have a good safety profile. Sublingual zolpidem (Intermezzo), the most recent entry in the class, has a 2.5-hour half-life and can be used for middle-of-the-night insomnia if patients have at least 4 hours left in bed. Zaleplon (Sonata) has a 1-hour half-life and can also be used in the middle of night, Dr. Parish said at a meeting on sleep medicine held by the American College of Chest Physicians.

The Z-drugs, along with short- to intermediate-acting benzodiazepines and ramelteon (Rozerem), are first-line options for insomnia, according to American Academy of Sleep Medicine guidelines (J. Clin. Sleep Med. 2008; 4:487-504).

Benzodiazepines with longer half-lives and active metabolites should be avoided for insomnia, Dr. Parish said. These agents can cause daytime sleepiness and cognitive impairment, among other problems, especially in elderly people less able to metabolize them.

After months or years of long-acting benzodiazepine use, rebound insomnia is an issue, as well. Patients stop the medication and "boom, their sleep is worse than ever for a week or two" before normalizing. The problem can keep "patients taking these drugs for years and years," Dr. Parish said.

So it's important to let patients know beforehand about the rebound potential, and tell them "that it's going to be bad for a while, but don't panic. Things will [get] better," he said.

Ramelteon, a melatonin receptor agonist, "is another useful drug." With no affinity for benzodiazepine receptors, it should not cause daytime drowsiness, he said.

Ramelteon metabolizes in the liver, so it can't be used in patients with liver disease. It also increases concentrations of alcohol, azole antifungal drugs, and fluvoxamine, and decreases rifampin levels.

"You have to think about how it's going to affect other drugs. Given that, I think it's a reasonably effective, reasonably safe drug," Dr. Parish said.

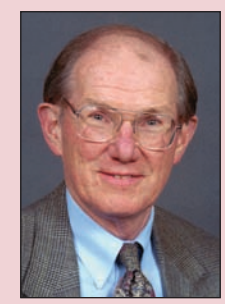
Because they have anticholinergic and antihistaminic effects, some antidepressants are insomnia options, too, but not as first-line agents and at doses lower than those used for depression.

The tricyclic antidepressant doxepin (Silenor) was approved for insomnia in 2010 at 3-mg and 6-mg doses, but it cannot be used with monoamine oxidase inhibitors.

Follow-up is important with all insomnia agents to assess effect and safety and to monitor for dose escalation. Concomitant cognitive-behavioral therapies – stimulus control and sleep restriction, for example – are helpful as well, with the goal of tapering patients off sleeping pills as behavior therapy takes effect.

Dr. Parish said he had no relevant financial disclosures. ■

COMMENTARY



Dr. Paul Selecky, FCCP, comments: This is important information for those who prescribe hypnotics. Not all sleeping pills are alike.

Judge Calls Cigarette Warnings Unconstitutional

BY FRANCES CORREA
Elsevier Global Medical news

The federal regulation requiring tobacco companies to display graphic antismoking images on cigarette packs is unconstitutional, a district judge in Washington, D.C., ruled.

"For corporations as for individuals, the choice to speak includes within it the choice of what not to say," Judge Richard J. Leon, district judge for the District of Columbia, wrote in the court memorandum. "The Government may engage in advocacy using its own voice, [but] it may not force others, such as Plaintiffs, to serve as its unwilling mouthpiece."

COURTESY U.S. FOOD AND DRUG ADMINISTRATION

Five tobacco companies – R.J. Reynolds Tobacco Company, Lorillard, Commonwealth Brands, Liggett Group, and Sante Fe Natural Tobacco Company – brought suit against the regulations in August 2011.

The Food and Drug Administration unveiled the nine graphic labels in June 2011, after proposed labels and associated regulations were available during a public comment period. Graphic images included a man breathing through an oxygen mask, a cadaver, a woman weeping, a mouth with what appears to be cancerous lesions, and a drawing of a premature baby in an incubator.

Under the regulation, cigarette manufacturers would be required to display one of nine textual warnings on all cigarette packages. Warnings include: "Smoking can kill you" and "Cigarettes are addictive." While the court recognized the government's right to require certain disclosures for clarity, Judge Leon ruled that "purely factual and uncontroversial information may still violate the First Amendment if they are unjustified and unduly burdensome."

The judge's ruling spurred vehement reaction from traditional tobacco opponents. "Judge Leon's dangerous ruling blatantly ignores significant scientific evidence supporting the effectiveness of larger, graphic warning labels in communicating the health dangers of tobacco use," said a statement by the American Academy of Pediatrics. "If allowed to stand, this ruling would make it impossible to implement any effective warning labels and will therefore harm the health and well-being of millions of children."

The Obama administration vowed to continue pursuit of the warnings.

"This administration is determined to do everything we can to warn young people about the dangers of smoking, which remains the leading cause of preventable death in America," said a statement from the Department of Health and Human Services. "This public health initiative will be an effective tool in our efforts to stop teenagers from starting in the first place and taking up this deadly habit. We are confident that efforts to stop these important warnings from going forward will ultimately fail."

Rep. Henry Waxman (D-Calif.) also criticized the decision.

"These provisions were informed by scientific evidence showing that current warning labels have run their course and that labels with graphic warnings would be more effective in protecting the public's health from tobacco's addictive and toxic qualities," Rep. Waxman said in a statement. "Congress did, in fact, carefully consider the First Amendment issues involved and carefully tailored the legislation to ensure the FDA could act as it has proposed with graphic warning labels for tobacco products."

Rep. Waxman said he expects the ruling to be appealed and its constitutionality affirmed. ■

COMMENTARY

Dr. Vera DePalo, FCCP, comments: Marketing of tobacco to children is still a major problem. This court decision strikes down what would have been a powerful tool for avoidance of tobacco use in children and young adults, under the umbrella of the First Amendment's "choice to speak ... and what not to say." While the image of the healthy individual on horseback and a movie or television show's depiction of young and healthy people at a party has been a longstanding marketing tool for tobacco use, one question remains: What happened to truth in advertising? This judicial action underscores the fact that our advocacy efforts against tobacco use will have to continue.

PRESIDENT'S CORNER

Legislative and Regulatory Changes in Health Care

BY DR. ROBERT ARANSON, FCCP; DR. ALAN M. FEIN, FCCP; AND SHARMI MAHAJAN, LLM, JD, MPH

Not since the passage of Medicare in 1965 will there be such sweeping health-care reform as from passage of the Patient Protection & Affordable Care Act (ACA) and the health care provisions of the Health Care & Education Reconciliation Act (HCERA) of 2010, collectively known as the Health Reform Law (HRL), signed into law by President Barack Obama. This legislation covers a huge breadth of health-care topics, including affordability, access, quality, fraud and abuse prevention, tax reform, and the mandate for all Americans to carry health insurance. To date, under the HRL, coverage has been expanded for young adults, increased for drug coverage for seniors hitting the "doughnut hole," and introduced to provide greater protections against insurance denial related to preexisting medical conditions.

The HRL is also affecting the way in which hospitals conduct and physicians practice health care. Thus, many physicians and the lay public have legitimate concerns about the HRL, as they did in 1965 with Medicare. The behemoth 2,700-page HRL is the largest and most expensive health-care legislation in American history, with the insurance coverage provisions projected to gross $1.762 trillion (net $1.252 trillion) in costs from 2012 to 2022 (Congressional Budget Office, Estimates for the Insurance Coverage Provisions of the Affordable Care Act, March 2012). With its immense size, scope, and cost, and its many sections that are scheduled to be activated in 2014, when the HRL is slated to be fully implemented, it is understandable that a significant number of American citizens and physicians are concerned.

While some aspects of the HRL have already been enacted, what follows is a partial list of major changes to the law that will affect hospitals and physicians:

1. Value-Based Purchasing for Physicians, Physician Groups, and Hospitals. Beginning in 2015, the Department of Health & Human Services (HHS) will establish a budget-neutral payment modifier to determine remuneration based on quality of care provided compared with cost. Physicians practicing in rural and underserved areas will be given special consideration. As for hospitals, a percentage of Medicare payments for some common, high-cost procedures (eg, cardiac, surgical, and pneumonia care) will also be bound to quality measures.

2. Hospital Readmission Reduction Program. Hospitals that participate in the Medicare Inpatient Prospective Payment System (IPPS) will be subject to monetary penalties if their readmission rates for certain conditions exceed a certain threshold. The diagnoses for initial scrutiny of recidivism will include myocardial infarction, heart failure, and pneumonia. Hospitals with readmission rates adjusted for high severity, which have not taken steps to reduce their recidivism, will be mandated to establish a Quality Improvement Program via existing patient safety organizations. Hospitals will be required to submit their data to HHS, which will be posted on the HHS website.

3. Quality Reporting for Long-term Care Hospitals, Inpatient Rehab Hospitals, and Hospices. Starting in 2014, these entities will be required to submit certain quality data or else face payment reductions of 2%.

4. Public Reporting of Physician and Hospital Performance: The Physician and Hospital Compare Websites. Starting in 2013, the public will be able to view comparative information on physician performance measures and assessments from the Physician Quality Reporting Initiative; patient health outcomes and functional status; continuity and coordination of care; efficiency; patient experience, as well as engagement of the patient, family, and caregiver; and effectiveness, safety, and timeliness of care. Public reporting of hospital data will be online via the Hospital Compare website.

5. Hospital-Acquired Conditions. Medicare reimbursement penalties will be imposed on hospitals with high rates of conditions or infections acquired while in the hospital, as of FY 2015. (Similar policies will be established for other Medicare providers, such as ambulatory surgical centers, nursing homes, long-term care facilities, health clinics, and others.)

6. Medicare Shared Savings Program. Eligible Medicare providers, including hospitals and vendors, may participate in an Accountable Care Organization (ACO) that ostensibly will save Medicare costs by incentivizing collaborative and coordinated care among its providers to increase accountability for quality health outcomes. Federal regulations are being proposed to establish payment models for ACOs, the Department of Justice and Federal Trade Commission are reviewing policies regarding antitrust laws with respect to ACOs, Internal Revenue Service rules are being examined for ACOs that would be tax-exempt or have 501(c)3 status, and the Office of the Inspector General and Centers for Medicare & Medicaid Services (CMS) is formulating rules for certain waivers for ACOs.

7. Disproportionate Share Hospitals (DSH). DSH payments help certain hospitals offset costs of care provided to uninsured patients. Beginning in 2014, for some hospitals, the majority of Medicare and Medicaid payment cuts will occur in the form of reductions to DSH payments, as the anticipated number of uninsured patients declines.

8. Market Basket Reductions. The annual market basket payment updates to hospitals, inpatient rehab facilities, nursing homes, home health-care providers, and others will be reduced.

9. CMS Innovation Center. Established in November 2010, the CMS Innovation Center tests health-care delivery and payment systems that support best-care practices and their dissemination, which are aimed at reducing Medicare and Medicaid costs and improving health care. Initiatives include testing of bundled payment models for acute, postacute, and chronic care; reducing hospital readmissions by 20% and nosocomial infections by 40% by 2013; supporting ACO development; fostering primary and patient-centered care; and granting monetary awards for health-care entities that rapidly implement innovative reformed delivery systems.

10. Fraud and Abuse Laws. The Stark and anti-kickback laws are strengthened, along with integrity provisions, across Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

11. Transparency Reports and Reporting of Physician Ownership or Investment Interests. Beginning March 31, 2013, and yearly thereafter, manufacturers of drugs or biological or medical supplies that provide payment or other value transfer over $10 to a physician or a teaching hospital will be required to submit reports on these payments/transfers to HHS, which will be publicly displayed on the CMS website. Additionally, manufacturers and group-purchasing organizations (GPOs) that deal with the aforementioned items must report certain physician ownership or investment interests in the manufacturer or GPO.

12. Electronic Health Records (EHRs). Under the American Recovery & Reinvestment Act (ARRA) of 2009 comes the Health Information Technology (HIT) & Electronic Health Records legislation with its subset of laws, referred to as the Health Information Technology for Economic & Clinical Health Act (the HITECH Act). Although not part of the HRL, Medicare-eligible providers also will feel the effects of this legislation. In 2011, the HITECH Act established incentive payments for eligible health-care providers and hospitals to initiate "meaningful use" of interoperable health information technology and qualified EHRs. Eligible providers could receive up to $44,000 over 5 years from Medicare and up to $63,750 over 6 years from Medicaid. Beginning in 2015, Medicare-eligible providers who do not demonstrate "meaningful use" of an EHR will be subject to a payment "adjustment" in their Medicare reimbursement.

13. Challenges to the HRL Before the Supreme Court. On March 26, 2012, the Supreme Court began to hear arguments regarding the constitutionality of the HRL minimum coverage requirement (ie, the mandate for every person to obtain health insurance). Related to this is whether the Supreme Court must wait until the first penalty is charged against an individual who does not comply with this mandate, or whether the Court can decide the mandate's constitutionality now. If the Court invalidates the mandate for minimum coverage, it must also decide whether the rest of the act, a portion of the act, or none of the act should be invalidated with it. Finally, the Court will need to decide on whether the states are being unconstitutionally coerced by the HRL mandate to expand Medicaid coverage.

In a legislative sea of perpetual changes, uncertainty surrounds the HRL and, in turn, how physicians should respond to it, especially given this presidential election year and the anticipated decisions from the Supreme Court. So where does that leave us? It is like sailing in a fog as thick as pea soup, with the wind blowing in one direction and the tide ripping in another, as we attempt to navigate uncertain waters, trying to dodge ledges that are seemingly everywhere, all the while hoping to site a beacon of light to guide us safely to our anticipated destination—higher quality health care that is efficient and nonburdensome for us to deliver and for our patients to receive, and just compensation for our services.

The ACCP, through the work of our standing committees, is taking an active role to ensure that the chest physician's perspective is represented. We welcome and greatly encourage your participation and feedback. ■

Health-care Reform: Is Anyone Listening?

This is the second in the series of articles focused on health-care reform (HCR). It focuses on legislative and regulatory changes that confront physicians, hospitals, health-care providers, and patients. The authors are Dr. Robert Aranson, Chair of the ACCP Chest Medicine Affairs Committee; Dr. Alan Fein, ACCP Governor for New York State; and Ms. Sharmi Mahajan, LLM, JD, MPH, Senior Policy Analyst at the ACCP. It is truly a monumental task to distil the essentials of this reform into one page of easily assimilable facts, and the authors must be commended for doing so. Through a series of seven monthly articles, scheduled to appear in *CHEST PHYSICIAN*, the ACCP will attempt to provide its members as much information as possible about these changes, some of which are already instituted and others that will be imminently enforced.

–Dr. Suhail Raoof, FCCP

Critical Care Commentary

Tele-ICU: A 'Field of Dreams' It Is Not

The movie "Field of Dreams" (1989, Universal Studios©) portrays a fantasy story of how a novice farmer builds a baseball field in rural Iowa at the behest of legendary baseball ghosts. Presumptively, from the ghosts he hears statements "build it and he will come," "people will come," and the closing scene suggests "build it and they will come" because cars are lined up into the horizon. There are significant financial challenges faced by this agrarian family, so the closing scene alluding to reward based on the central message of having faith in building something and reaping benefits without a plan might resonate with many. Electronic medical record (EMR) systems, in general, and, specifically, tele-ICU programs that have taken an approach similar to "build it and they will come" have not seen significant outcomes, in contrast to robust process re-engineering implementations.

Tele-medicine is defined as the diagnosis and treatment of patients in remote areas using medical information, as radiographs or television pictures, transmitted over long distances, especially by satellite. Logically, tele-ICU systems provide off-site critical care expertise via video and audio conferencing equipment, facilitating optimal utilization of informational, technological, and clinical systems. Most tele-ICU systems have unidirectional or bidirectional video and audio communications, an EMR, and some might use severity-adjusted benchmarking models. Tele-ICU systems have been described since the 1970s and generally can be grouped into three models. A reactive implementation would include consultations provided by remote clinicians only when solicited, and this model would use unidirectional or bidirectional video and audio and some mechanism to review physiologic trends and laboratory values. An intermediate model could include robotic-controlled audiovisual carts and concurrent access to local EMR resources. Robotic carts have limited video functionality due to a combination of Wi-Fi networks and a lower profile that might disallow optimal patient viewing. The most implemented model includes clerical and expert critical care clinical staff at a dedicated location with multiple tele-ICU workstations. Proprietary systems include a unique EMR, early alert analytic systems designed to detect physiologic instability, bidirectional video and audio communication pathways, and help buttons conveniently located in each ICU room. Nearly all current tele-ICU programs utilize a proprietary system that, as of 2010, accounted for over 5,500 critical care beds at over 200 hospitals, caring for about 12% of the critically ill in the United States (www.nehi.net/uploads/full_report/teleicu_critical_care_critical_choices.pdf).

There are at least two major driving forces promulgating tele-ICU programs. Hospitals are under increasing pressure from regulatory agencies and payers to adopt an ICU physician staffing (IPS) program as described by the Leapfrog Group (www.leapfroggroup.org/media/file/Leapfrog-ICU_Physician_Staffing_Fact_Sheet.pdf; accessed March 9, 2012). There is general consensus that adopting IPS standards will decrease mortality, morbidity, and costs associated with caring for critically ill patients (Dimick et al. *Crit Care Med*. 2001;29[4]:753; Pronovost et al. *Crit Care Med*. 2004;32[6]:1247). Many smaller hospitals are unable to afford a dedicated intensivist team but, more importantly, they are not able to recruit intensivists, partly due to shortages. Therefore, many hospitals are adopting tele-ICU programs to help mitigate issues by on-site intensivist deficits. The other major factor relates to mixed but favorable evolving tele-ICU outcome literature.

To date, there have been over 100 unique literature contributions pertaining to tele-ICU (Young et al. *Arch Intern Med*. 2011;171[6]:498); however, only 14 could be considered at least level two studies. Young and colleagues performed an extensive literature search of published studies on tele-ICU programs and found 13 studies that had acceptable rigor. None of the published study designs had a concurrent control arm, and all were preimplementation and post-implementation comparison variants. About half of those studies contained both ICU and hospital mortality and length of stay (LOS) outcome measures. The pooled data represented 35 ICUs, over 15,000 and 25,000 baseline ICU and tele-ICU patients, respectively. Their findings suggest that ICU mortality is statistically lower (odds ratio [OR] 0.80, 95% confidence interval [CI] 0.66 to 0.97) and that there is a trend toward lower hospital mortality (OR 0.82, 95% CI 0.65 to 1.03). LOS data are less robust; however, ICU LOS significantly decreased by a standardized mean difference (SMD) of –1.26 days (95% CI –2.21 to –0.3), and there is a trend toward decreased hospital LOS SMD by –0.64 (95% CI –1.52 to 0.25). After excluding studies with vendor affiliation, ICU mortality significance erodes but still trends favorably (OR 0.87, 95% CI 0.7 to 1.08); however, ICU LOS advantage abates (SMD 0.05, 95% CI –0.05 to 0.16).

An extensive review article (Lilly and Thomas. *J Intensive Care Med*. 2010;25[1]:16) discloses less rigorous data representing 26 ICU before and after study designs. Standardized mortality ratios (SMR) and LOS were calculated on individual and pooled data using Acute Physiology and Chronic Health Evaluation III (APACHE III) scoring systems. A total of 88% of tele-ICU implementations saw improved LOS, and 81% saw at least a 10% reduction in SMR. A more recent unblinded step wedge trial design tele-ICU study found significantly improved processes of care, decreased complications, and improved adjusted mortality and LOS (Lilly et al. *JAMA*. 2011;305[21]:2175). When a tele-ICU program is implemented at an academic medical center as an additional tool for a described critical care delivery model (McCauley and Irwin. *Chest*. 2006;130[5]:1571), Lilly and colleagues found: (1) adjusted hospital mortality significantly decreased (OR 0.40, 95% CI 0.13 to 0.52); (2) higher rates of best practice adherence for prevention of deep vein thrombosis (DVT) (OR 15.4, 95% CI 11.3 to 21.1) and prevention of stress ulcers (OR 4.57, 95% CI 3.91 to 5.77) and cardiovascular protection (OR 30.7, 95% CI 19.3 to 49.2) and prevention of ventilator-associated pneumonia compliance (OR 2.20, 95% CI 1.79 to 2.70); (3) lower rates of ventilator-associated pneumonia (OR 0.15, 95% CI 0.09 to 0.23) and catheter-related bloodstream infection (OR 0.50, 95% CI 0.27 to 0.93); (4) shorter hospital LOS (hazard ratio for discharge 1.44, 95% CI 1.33 to 1.56).

In summary, there is a growing body of literature suggesting that tele-ICU implementations are associated with ICU and hospital mortality decreases, ICU and hospital LOS decreases, and that these effects might be attributed to increases in best practice adherence, earlier detection of physiologic instability, and complication decreases.

It is important to note that not all implementations have experienced improved outcomes; in fact, some have experienced either no change in SMR or LOS or have seen increased SMR ratios and increased LOS. Two larger controlled trials failed to show statistical significance in their primary outcomes (Morrison et al. *Crit Care Med*. 2010;38[1]:2-8; Thomas et al. *JAMA*. 2009;302[24]:2671); however, many feel that these two studies failed because the intervention was used in less than 40% of patients.

What is lacking in the literature is any indication as to which specific elements of tele-ICU programs are critical to success. One would posit that video and audio communications would be integral, but this is not known. Is it early detection of physiologic instability or reengineering processes to increase best practice adherence that infer decreased complications or some other factor? Many opinions abound, and a recent research agenda was proposed by the Critical Care Societies Collaborative that recommends a Donabedian framework dissecting out structure, process, and outcome components (Kahn et al. *Chest*. 2011; 140[1]:230).

Tele-ICUs are likely here to stay, largely, in part, due to financial pressures, intensivist staffing challenges, and evolving data supporting improved ICU and hospital mortality and probably LOS. However, a cautionary note must be emplored—implementations using a "Field of Dreams" approach will likely prove to be an expensive failure. ■

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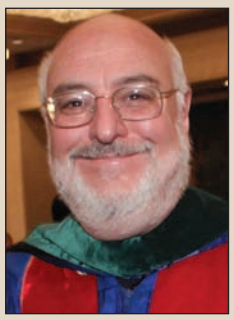

Editor's Comment

The very thoughtful and evocative commentary by Dr. McIlwaine brings the crux of the issue to the forefront. Tele- or e-ICU can be a potential solution for some of the most perplexing issues in critical care, ie, the increasing demand by the patients, lack of trained providers, and adaptation of current standards. Despite the growing literature and anecdotal reports of success, exactly which parts or types of e-ICU are truly helpful is unclear. The fact that critical care continues to consume larger chunks of the medical dollar, further expenditures without proven benefits either in cost or patient outcomes make widespread adaptation of e-ICU still a ways off. I hope the ongoing studies will continue to shed light and direction on these questions. I believe this commentary section will be revisiting this issue in the year to come.

–Dr. Peter Spiro, FCCP

CHEST 2011 CENTERS OF EXCELLENCE SERIES

DASH-Discharge + Assessment & Summary @ Home

BY DR. BRIAN CARLIN, FCCP

The following is the first of a series of articles discussing presentations that were given at the CHEST 2011 Centers of Excellence in Honolulu, Hawaii. This program was presented by Dan Easley, Chief Business Development Officer, Klingensmith HealthCare, and Dr. Brian Carlin, FCCP.

Improving the transition of care for the patient with COPD from hospital to home and reducing the 30-day rehospitalization rates following exacerbations are strategies that have matured from a "think tank" status to an operating reality for many American hospital systems. The Patient Protection and Affordable Care Act of 2010 has dramatically increased the emphasis on managing a patient's transition from the hospital to home environment. Respiratory therapy plays a pivotal role in managing this transition for a patient with COPD.

One program, available in Western Pennsylvania (DASH-Discharge + Assessment & Summary @ Home, Klingensmith HealthCare, Ford City, Pennsylvania), focuses on high touch, intensive respiratory services for patients with COPD following their hospitalization for COPD exacerbations. This program was designed to incorporate various critical components (eg, physical/clinical assessment, environmental assessment, medication management, equipment management, education, establishment of motivational goals, and measurement of outcome metrics) to help manage such patients.

The program is implemented prior to hospital discharge and incorporates over 20 points of contact over the first 30 days following hospital discharge. The key to the program is face to face visits by a respiratory therapist in the patient's home. During these visits, the therapist helps the patient to understand risk factors, teaches self-management skills, reviews medication use, establishes physician follow-up and rehabilitation appointments, titrates oxygen during home activities, measures clinical/motivational attributes, and tracks use/adherence data.

To date, over 550 patients have been enrolled into the program from 23 hospitals. These patients had COPD and required home oxygen therapy following their hospital admission. The overall 30-day readmission rate for the group is 5% (vs a historical rate of 24% in western Pennsylvania). Analysis of the results of a subgroup of patients who were hospitalized with an exacerbation of congestive heart failure requiring home oxygen therapy and enrolled into the program showed a similar 30-day rehospitalization rate of 5%. The results are measured using clinical best practices as promoted by the Physician Consortium for Performance Improvement and HEDIS measures. Several abstracts regarding the program have been presented at recent ACCP, AARC, and ATS meetings.

Strategies to reduce hospital readmission rates following an exacerbation of COPD will need to be developed in order to provide the best care possible for such patients. Various strategies have been developed throughout the country. This program has successfully integrated the respiratory therapy team into the transition of care process for such patients. ■

Award Recipient's Project Knows No Boundaries

The work of Dr. Dee Ford, MSCR, FCCP, 2010 recipient of the Roger C. Bone Advances in End-of-Life Care, is having a far-reaching impact, from the Medical University of South Carolina (MUSC) to the ACCP Simulation Center at CHEST 2011, and beyond. Her project, "Integrating an End-of-Life Communication Curriculum Into Pulmonary/Critical Care Training," utilizes the study "Improving Clinician Communication Skills (ICCS)" and is built on adult-learning principles that emphasize experiential learning through interaction with simulated patients to practice communications skills.

At MUSC, where Dr. Ford serves as Associate Professor, she has developed a program to bring together the interprofessional team in the ICU. This systematic approach ensures that physicians and nurses, along with spiritual and psychosocial professionals involved in the care of the patient, "huddle" before an ICU family meeting. "While the ICU can be extremely hectic," Dr. Ford comments, "you should never be too busy to spend time with the family of a critically ill patient. This is especially true when you expect the patient might not survive. The family will remember that experience the rest of their lives." The passionate professionals at MUSC have embraced making communication an explicit part of their training and strive to integrate effective communication into routine ICU culture to the benefit of families and patients.

The simulation session, "Critical Conversations in Palliative Care: A Comprehensive Approach to Communicating Patient Care," reached a wide and diverse audience at CHEST 2011. This hands-on learning opportunity is co-chaired by Dr. Ford and Dr. Daniel Ray, FCCP, 2006 Roger C. Bone Advances in End-of Life Care Award recipient. Dr. J. Randall Curtis, FCCP, recipient of this award in 2001, served as faculty for this session. The session brought together world-renowned experts from various fields, including critical care, oncology, and pediatric palliative care. Through this opportunity, fellows and medical students gained skills needed for optimal patient care and family communication. This essential skills training will be replicated in future courses.

COURTESY ACCP

Dr. Ford with some colleagues.

The Roger C. Bone Advances in End-of-Life Care Award was established in 1999 to recognize an ACCP member who demonstrates outstanding leadership in end-of-life care. This award honors the late Roger C. Bone, MD, Master FCCP, who wrote about the ethical and humanistic issues surrounding communication among physicians and their patients.

For Dr. Ford, receiving this nationally recognized award carries tangible and intangible value. Those who receive this acknowledgment from The CHEST Foundation also receive acknowledgment at their institutions and in their careers. However, first and foremost for Dr. Ford, it is about the work and not the recognition. "I was tremendously honored to have received this important award from The CHEST Foundation. Yet, ultimately, the reward comes from the work I do with patients and families and the physicians-in-training who I can influence. Recently, I had an amazing experience where my efforts at training our fellows in principles of end-of -life communication came full circle back to me. A physician from a referring hospital commented to me that one of our recently graduated pulmonary fellows was working at his hospital. He noted that our fellow "really knew how to talk to families about end of life" and that this former fellow responded, "It's one of the most important parts of my job."

The Foundation offers ACCP members opportunities to apply for a variety of awards in the areas of clinical research and humanitarian service. The CHEST Foundation awards have supported ACCP members early in their careers, as well as those Distinguished Scholars whose innovations have the impact to transform clinical care and save lives. Learn more about The CHEST Foundation 2012 Awards Program below and at OneBreath.org, or contact Lee Ann Fulton at lfulton@chestnet.org. ■

The CHEST Foundation Awards Program 2012

May 4 Deadline Approaching

The CHEST Foundation provides funds for volunteer service, leadership, and clinical research through its annual awards program. In 2012, awards are offered in critical care, end-of-life care, women's health, COPD, pulmonary arterial hypertension, lung cancer, and humanitarian service. The CHEST Foundation offers 1-, 2-, and 3-year awards for ACCP members' projects.

► **Fourth Eli Lilly and Company Distinguished Scholar in Critical Care Medicine award** is open to ACCP members who are FCCPs. The individual selected as Distinguished Scholar would develop an original education project that will help disseminate new knowledge about critical care medicine and advance the creation of best practices in patient care. The recipient would investigate innovative treatment of critical care patients and create, manage, and evaluate a project over a 3-year period. This award is intended to fund the investigation of issues that are not easily supported through traditional funding. The award grants $150,000 over the course of 3 years.

► **Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency.** This 1-year $25,000 award supports research focused on COPD and AAT deficiency. Research projects primarily in usual COPD (not associated with AAT deficiency) are allowed. Projects with a focus on AAT deficiency are encouraged.

► **The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women's Lung Health and The Sheila J. Goodnight, MD, FCCP, Clinical Research Award in Women's Lung Health (NEW).** These two, 1-year $10,000 awards support clinical researchers' projects related to women's lung health, which may include research on gender differences in various lung diseases, such as COPD and lung cancer. The Sheila J. Goodnight Clinical Research Award in Women's Lung Health was established this year in memory of Dr. Goodnight who passed away in October of 2011. Dr. Goodnight served as Professor of Medicine and Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine at the Michael E. DeBakey VA Medical Center in Houston. She was a physician-scientist and exceptional teacher in the undergraduate medical curriculum. Among many leadership roles within the ACCP, she served as chair of the Women's Health NetWork.

► **The CHEST Foundation California Chapter Clinical Research/Medical Education Award.** This award supports a $5,000, 1-year clinical research or medical education project proposed by an ACCP member who lives in California. Candidates must be members of the ACCP and hold the degree of MD, DO, MBBCh, PharmD, PhD, or its equivalent.

► **OneBreath® Clinical Research Award in Lung Cancer.** This 2-year $100,000 award ($50,000 annually) supports a project that is focused on medical and/or surgical detection, and treatment of lung cancer that is based on clinical and/ or translational research. Applicants must be ACCP members who have completed at least 2 years of pulmonary or critical care fellowship or a thoracic surgery residency and be within 7 years of completing training.

► **The CHEST Foundation Clinical Research Award in Pulmonary Arterial Hypertension (NEW).** This 1-year $50,000 award supports an outstanding researcher in the formative stage of his or her career who proposes an innovative PAH research project. This award is new for 2012 and has been established through a generous grant from Actelion Pharmaceuticals, US, Inc. Applicants must be ACCP members who have completed at least 2 years of pulmonary or critical care fellowship and be within 7 years of completing training.

► **The CHEST Foundation continues its support of leadership in end-of-life care through the Roger C. Bone Advances in End-of-Life Care Award.** This 1-year award of $10,000 supports an ACCP member's project that stresses importance of communication, compassion, and effective listening. The award is given for leadership in end-of-life care—on the international, national, or local level—and does not fund research or provide seed money for new end-of life or palliative care programs or projects.

► **The D. Robert McCaffree, MD, Master FCCP Humanitarian Awards** support the volunteer efforts of those who give time and expertise to improve the health of people in communities throughout the world. The award provides funds to nonprofit and nongovernmental organizations where ACCP members give pro bono service. The CHEST Foundation will grant awards in amounts of $5,000, and up to $15,000, to a total of $50,000 in 2012. In addition, the $5,000 Ambassadors Group Humanitarian Award will be given as part of this program. As an example of the types of programs The CHEST Foundation seeks to fund, recent past recipient organizations include: The Free Medical Clinic of Greater Cleveland Volunteer Pulmonary Clinic, Cleveland, Ohio; Living Extreme With Cystic Fibrosis Documentary, Cystic Fibrosis Lifestyle Foundation, Burlington, Vermont; Project S.I.E.S.T.A (Students Involved in the Education About Sleep Hygiene for Teen Adolescents), Houston, Texas; Sustainable Health Promotion for the Indigent of Belin, Peru.

The CHEST Foundation Awards Committee encourages ACCP members to take advantage of this important member benefit by applying for an award in their areas of expertise. Learn more and apply for an award at OneBreath.org. The application deadline for all awards is May 4, 2012.■

FROM THE EVP/CEO

Spring Leadership Meeting

I would like to take this opportunity to provide you with an update on the direction of the ACCP and some outstanding programming on which we've embarked.

Having just completed our 2012 Spring Leadership Meeting (formerly called the Spring Board of Regents Meeting), I am happy to report some major progress in our leadership development activities and strategic planning.

PAUL A. MARKOWSKI, CAE

Under the leadership of your President, Dr. Suhail Raoof, FCCP, and direction of the Leadership Development Task Force, co-chaired by COL Lisa Moores, MC, USA, FCCP, and Dr. Kay Guntupalli, FCCP, we launched the beginning of a newly structured and systematic learning program for our current leadership, potential leaders, and any volunteers who are passionate about guiding the ACCP today and into the future.

Our 2012 Spring Leadership Meeting kicked off with a joint session of all leadership—Board of Regents, Board of Trustees, Chairs, and Vice-Chairs of committees. Dr. Raoof and I provided a "State of the Association"; Mary Byers, co-author of *Race for Relevance,* enlightened the attendees with a presentation focusing on crucial issues faced today by professional associations, such as the ACCP; and Susan Decker of BoardSource, Inc, provided the group with organizational governance education and guided the attendees through strategic planning. It was an incredible day!

Ms. Byers provided six key points about how to face the future that are relevant to any professional society and to all physicians as members of a practice plan, hospital, or other health-care delivery system. All organizations should be assessing these ideas today.

▶ **Different times require different leadership (leadership skills).** Leaders should be discussing issues more, voting less, and assessing their processes, including their committee structure. Focus on the big issues, and don't get stuck in the weeds.

▶ **Be future-focused.** Focus on setting up successful systems for those who follow you. Does your organization have the right resources, including technology? The College is investing in an association management system to better meet member needs. Hospitals are investing in electronic health records. Most importantly, focus on your greatest potential for growth. For the ACCP, that is our educational expertise.

▶ **Govern vs manage.** Ideally, your board should be focusing at the 30,000-foot level (management level). Managing is easier as it involves short-term decisions, often involving fewer choices and fewer individuals; governing (the Board's role) takes greater discipline and requires looking at the big picture to make strategic decisions positively impacting multiple member constituencies.

▶ **Focus on why.** When you know the why of what you plan to do strategically, you are more likely to know the way of doing it with greater clarity.

▶ **Focus on sustainability of your organization.** How have ACCP members changed over time (your medical staff members)? Think about generational differences—baby boomers vs generation X. Does this mean the ACCP model needs to change? Will the revenue stream change? Will generation Xers participate in the same way as our current volunteers?

▶ **Be radically courageous.** Don't be afraid of letting go of what is not working. Eighty percent of the value of an organization often comes from 20% of the projects being pursued. The greatest potential for growth comes from what you are already doing well. For the ACCP, that is the educational opportunities we provide to you as a valued member.

As you can see, the ACCP is heading into a thought-provoking, new direction on leadership development and governance education. The participants at the Spring Leadership Meeting were fully engaged and actively participated in a long day.

This is just the first step. The Leadership Development Task Force has laid out a plan for the future that will deliver this type of enrichment to many more members and future leaders at forthcoming CHEST meetings and other educational venues.

Stay tuned! More exciting information will follow. ■

Paul

In Memoriam

Dr. Irwin Berlin, FCCP, died in March 30, 2012. His funeral was held Monday, April 2, in New York. Dr. Berlin was Chief, Division of Pulmonary/Critical Care Medicine, Elmhurst Hospital Center, Elmhurst, NY. He was an active ACCP Fellow, serving previously as ACCP Governor for New Jersey and as a member of the former Government Relations Committee from 2001-2010, chairing that group from 2009-2010. He was a current member of the ACCP Chest Medicine Affairs group. Dr. Berlin once noted, "One of the highlights of my career was to represent ACCP, at the invitation from the Obama Administration, and participate in the Rose Garden signing ceremony for the Family Smoking Prevention and Tobacco Control Act." ■

The CHEST Foundation's OneBreath® Campaign Updates

Family Activities Toolkit Contest

Our second social media contest is currently taking place and runs through April 30, 2012. Individuals may enter the contest by liking OneBreath on Facebook and completing the contest entry form. The goal is to increase awareness of OneBreath, to encourage exploration of the Family Activities Toolkit, and to highlight the unique content of OneBreath.

OneBreath has gained nearly 500 new Facebook "likes" since the start of this new contest in March. Our current community is nearly 1,700 people and growing.

Content Editors and Contributors

OneBreath is seeking ACCP members who are interested in participating in the campaign as content editors and contributors for the OneBreath.org website. Content editors and contributors will help to enhance, edit, and seek out content related to the nine prevention areas of the campaign.

OneBreath Bloggers Needed

OneBreath is giving ACCP members the opportunity to become guest bloggers on its newly launched blog. Blog postings, 200- to 300-word articles, are meant for a patient audience.

If you are interested in joining as a OneBreath content editor, contributor, or blogger, or have a topic suggestion, please contact Kristi Bruno at kbruno@chestnet.org or call (847) 498-8308. ■

NETWORKS
Disaster Response Training, Radon, Asthma Literacy

Women's Health

Remembering Dr. Goodnight

In her charming southern drawl, Dr. Sheila Goodnight always knew the right thing to say. She had immense empathy for whomever she was talking to, whether it was a medical student, a resident, or a colleague. With these qualities, Dr. Goodnight was a friend, mentor, and guide to countless at the Baylor College of Medicine and within the ACCP community.

Prior to her death in October 2011, Dr. Goodnight had an extremely successful career as a physician scientist and administrator, serving as the Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine at the Michael E. DeBakey VA Medical Center in Houston, Texas. A leader in medical education at the Baylor College of Medicine, she served as Vice-Chair for undergraduate education and Chair of the Curriculum Committee.

As a leader in the ACCP, Dr. Goodnight served as Chair of the Women's Health NetWork(WHN). The WHN was like her professional "family." She was "an incredibly involved and dynamic leader" and an "outstanding mentor" to many in the NetWork. She was an enthusiastic champion of the Community Outreach events held during CHEST. As one steering committee member remembered, "I was amazed at her ability to connect with people of all ages. Her enthusiasm, her passion, and her animation with that Texas flair was unparalleled. As many of us in the WHN and the ACCP miss her friendship, mentorship, and brilliant smile, we are delighted to know that her ACCP legacy will continue as The CHEST Foundation's Sheila J. Goodnight, MD, FCCP, Clinical Research Award in Women's Lung Health.

Those wishing to honor Dr. Goodnight's memory and her lifelong dedication to education can obtain information from Baylor on the Sheila Goodnight Endowed Fund in Medical Education (https://connect.bcm.edu/SSLPage.aspx?pid=456).

Dr. Surakanta Velamuri, FCCP
Steering Committee Member

Disaster Response

Simulated Disaster Response Training Gains Global Acceptance: PPE and Beyond

Simulation is starting to play a crucial role in disaster response and critical care education. Previously, 100 diversely trained registrants for the simulation experience at the annual CHEST meeting took a pretest on personal protective equipment (PPE) use and knowledge on chemical disaster agents. PPE is used during airway management with contagious respiratory tract illnesses or during chemical emergencies.

Studies conflict on the ability of personnel to expeditiously perform necessary procedures while wearing maximum PPE-Level A (Garner et al. *Emerg Med Australasia*. 2004;16[2]:108; Greenland et al. *Resuscitation*. 2007; 74[1]:119). Skill enhances with experience, but routine use is cumbersome. A lecture on PPE use and management of chemical victims was given. Performance in intubation, subjective PPE experience, and acute patient management were evaluated. This rapid learning session employed task trainers, human patient simulators, and case-based discussion to improve skills with initial management of acute respiratory decompensation in highly toxic/infectious victims. The course faculty included military instructors, clinicians with global disaster experience, and emergency airway management in critical care. The use of these techniques will have an impact in many critical areas (Subbarao et al. *Prehospital Disaster Med*. 2006;21[4]:272).

There is now a global move to incorporate simulation actively in disaster response education. As an example, the First National Conference on Simulation in Healthcare is being held in India in 2012, with sessions devoted to disaster training (www.tact-india.com/national-conference.html).

Alan Roth, RRT;
Dr. Asha Devereaux, FCCP;
Dr. Dennis Amundson, FCCP;
Dr. David Prezant, FCCP; and
Dr. Sai Praveen Haranath, FCCP

Occupational and Environmental Health

If There's Something Weird and It Doesn't Look Good

If you sense something spooky is going on in your home, you might want to call the Ghostbusters. But what if there was an invisible carcinogen in your home? Dr. Paul Blanc, FCCP, an Occupational and Environmental Health NetWork member, has posted on his *Psychology Today* blog about the hazards of radon (http://www.psychologytoday.com/blog/household-hazards/201112/the-iowa-isnt-in-the-news).

Radon, a decay product of uranium that seeps out of rocks and soil, is typically present in very low levels in ambient air. Radon decays, producing radioactive radon daughters that may contaminate the surface of respirable dust particles.

Radon is the second most common cause of lung cancer, after cigarette smoking, estimated to cause 21,000 deaths per year in the United States. Radon was linked to lung cancer more than a century ago among miners in central Europe and remains an occupational hazard in mining today. Domestic exposure occurs when radon gas moves through the ground into homes via cracks and holes in the foundation and gets trapped in poorly ventilated rooms, eg. the basement and attic. The highest US radon concentrations are in Iowa and in the Appalachian Mountains in southeastern Pennsylvania. Granite used in countertops and home construction also produce low levels of radon, depending on the composition of the molten rock from which it was formed.

If your patients wonder about radon in their homes, they can obtain radon test kits from local health departments, state radon programs, the National Radon Program Services (www.sosradon.org or 1-800-SOS-RADON), American Lung Association (www.lungusa.org), or some home improvement stores. They can also find a qualified testing or mitigation contractor by contacting their state radon office (www.epa.gov/radon/whereyoulive.html) or the national private radon programs (www.epa.gov/radon/radontest.html).

Dr. Ware Kuschner, FCCP

Palliative and End-of-Life Care

Mass Customization of Palliative Care

Dying cannot be scientifically studied since each person dies in his or her own unique way. In my experience, a few "give up the ghost" and die unexpectedly soon after being told of a terminal condition. Others linger way beyond any reasonable medical expectations. The same is true regarding palliative care. For some, suffering is readily controlled while for others no amount of interventions can control their suffering. This is why palliative and terminal sedation policies exist. This variability in dying and responses to interventions makes palliative care "both a philosophy of care and an organized, highly structured system for delivering care" (National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care,* Second Edition. Pittsburgh, PA: National Consensus Project, 2009). Unlike science, which has immutable laws like gravity, philosophies are based on unprovable premises. Palliative care has one comprehensive set of consensus premises, although there are no reasons competing premises cannot arise.

These circumstances require the mass customization of palliative care to the patient rather than the reverse. This N=1 conundrum arises because published evidence cannot prospectively predict any single patient's response to any specific intervention at any given moment. This unknown is why palliative care must adjust its care to the patient's unique responses at every moment since responses may vary from moment to moment. In summary, if it is to prevent and relieve suffering, palliative care be unique for each patient through the mass customization of its care delivery.

Dr. Fidel Davila, FCCP
Steering Committee Member

Respiratory Care

Asthma Literacy and the Asthma Community

The National Asthma Education and Prevention Program (NAEPP) guidelines that were initially published in 1991 were revised in 2007 (National Asthma Education and Prevention Program (NAEPP). *Expert Panel Report 3 (EPR3): guidelines for the diagnosis and management of asthma. Update on selected topics 2007*. Bethesda, MD: US Department of Health and Human Services; July 2007. www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 13, 2012.)

The guidelines are: initial assessment and diagnosis plus periodic assessment and monitoring; control factors that contribute to asthma severity; pharmacologic therapy; and education for a partnership in asthma care. Saville and colleagues (*Respir Care*. 2008;53[12]: 1691) measured childcare workers' asthma knowledge and ability to care for asthma exacerbations before and after training, an asthma core knowledge assessment of those within what we termed the "asthma community" (Masini and Krishnaswamy. *Respir Care*. 2008;53[12]:1665).

The asthma education clinic at East Tennessee State University embarked upon a physician-led deployment of health-care workers with the goal of increasing the literacy of those living within the "asthma community." The "asthma community" consisted of persons living with asthma and those who surrounded them, people who could assist them with asthma management, to include parents, babysitters, school nurses, teachers, coaches, clergy, and neighbors. Dr. Guha Krishnaswamy trained a respiratory therapist and asthma educator-certified (AE-C) and respiratory therapy students to provide asthma education to schools, malls, civic organizations, and faith-based groups, and together they prepared the "community" to better assist with strategies, such as improved housekeeping and indoor air quality, avoiding pollution and cigarette smoke, and monitoring and dealing with an emergency based upon an asthma action plan. Asthma training for community members strengthened the asthma action potential and improved asthma literacy regarding compliance with the physician-ordered regimen. Community education may provide new ways to address asthma morbidity and mortality, and all members of the asthma community benefit from increased asthma literacy.

Doug Masini, RRT
Steering Committee Member; and
Dr. Guha Krishnaswamy, FCCP

You Should Know About...

World Congress of Asthma

Make plans to attend the World Congress of Asthma, held August 18-21, 2012, in Québec City. Attendees can expect a superb educational and networking meeting where world-class speakers will offer an update on the epidemiology, physiopathology, clinical management, and various other aspects of care of children and adults with asthma. While there, be sure to attend the joint ACCP and Canadian Thoracic Society national society symposium on asthma and sleep. Learn more and register at http://www.wca-2012.com.

World Spirometry Day

The American College of Chest Physicians (ACCP) has joined with the Canadian Thoracic Society (CTS) and the American Thoracic Society (ATS) to participate in the World Spirometry Day 2012, an initiative organized by the Forum of International Respiratory Societies (FIRS). Since this is an Olympic year, the focus of this year's campaign is fitness and respiratory health. We invite all members of the ACCP, CTS, and ATS to join in this initiative to bring awareness to lung health and fitness by holding events promoting lung health and testing beginning on June 27th and continuing on up to the conclusion of the Paralympics, ending September 9. Learn more about World Spirometry Day in a personal message from the presidents of ACCP, CTS, and ATS at http://www.chestnet.org/downloads/bkellwsdltr-3.pdf. ■

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP
Editor in Chief

▶ **Fetal Exposure to Maternal and Paternal Smoking and the Risks of Wheezing in Preschool Children: The Generation R Study.** *By Dr. L. Duijts et al.*

▶ **Portopulmonary Hypertension: A Report From the US-Based REVEAL Registry.** *By Dr. Krowka et al.*

▶ **The Impact of Ischemic Heart Disease on Symptoms, Health Status, and Exacerbations in Patients With COPD.** *By Dr. A. R. C. Patel et al.*

POINT-COUNTERPOINT EDITORIAL

▶ **Should Pleural Manometry Be Performed Routinely During Thoracentesis?**
Yes – Dr. D. Feller-Kopman, FCCP
No – Dr. F. Maldonado; and Dr. J. Mullon

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE
February 2012 CPT® Editorial Panel Meeting

BY DIANE KRIER-MORROW, MBA, MPH, CCS-P
ACCP Coding and Reimbursement Consultant

NOTE: Please be aware that these actions are a reflection of the discussions at the most recent Panel meeting. Future Panel actions may impact these items. Codes are not assigned and exact wording is not finalized until just prior to publication. Release of this more specific CPT® code set information is timed with the release of the entire set of coding changes in the CPT publication.

At the February 2012 CPT Editorial Panel meeting, ACCP and ATS were the busiest ever with presenting five proposals. All attending CPT meetings sign confidentiality statements, and historically were not to inform its members of panel actions until the AMA CPT book was published. Just recently we became aware that AMA published the results of the February 2012 meeting on its website with the following link: http://www.ama-assn.org/resources/doc/cpt/summary-of-panel-actions-feb2012.pdf.

The membership should be aware of what codes will be added/revised/deleted of interest to pulmonary, critical care, and sleep medicine physicians in the coming CPT Changes for January 1, 2013. ■

Tab #	Title of Request	Description of Request	Description of CPT Editorial Panel Action
9	Chest Tube Thoracostomy Revision 32551	Request for clarification of intent for use of 32551 by 1) adding the word "open" to identify this as an open procedure, 2) to indicate "water seal" as an "e.g.", 3) to remove diagnosis terminology from the descriptor, 4) to remove references to imaging for this procedure as image guidance is rarely necessary, and 5) to remove the current diagram.	Accepted revision of code 32551 to specify the surgical approach and by deleting the diagnostic references.
10	Chest Tube Placement	Request for the establishment of four new chest tube placement codes (325X1-325X4); deletion of 32420, 32421, 32422; and the deletion of the 32421-32422 illustration.	Accepted establishment of four new codes for thoracentesis and pleural drainage (325X1-325X4), with deletion of codes 32420-32422.
22	Bronchography (Deletion of 31656, 31715, 71040, 71060)	Request to delete bronchoscopy code 31656, transtracheal injection code 31715, and bronchography radiological supervision and interpretation codes 71040 and 71060.	Accepted deletion of codes 31656, 31715, 71040, and 71060, as bronchography has now been replaced by use of computed tomography (CT).
70	Chest Wall Manipulation	Request for editorial revision of the initial and subsequent pulmonary manipulation chest wall therapeutic procedure codes 94667 and 94668 to include reference to another manual technique – frequency chest wall oscillation therapy.	Postponed until time uncertain. Reconsideration is requested and will be addressed at the May Panel meeting.
73	Pediatric Polysomnography	Request to establish codes 958X1X and 958X2X to report pediatric polysomnography for children 5 years of age or younger.	Accepted: 1) establishment of codes 958X1X-958X2X to report pediatric polysomnography for children younger than 6 years of age; 2) revision of code 95808 to include "any age" and codes 95810-95811 to include age specification "age 6 years or older."
85	Bronchial Thermoplasty	Request to convert Category III bronchial thermoplasty codes 0276T and 0277T to Category I status (codes 316X1, 316X2).	Accepted conversion of Category III codes 0276T and 0277T to Category I codes 316X1-316X2.
EXECUTIVE COMMITTEE	RUC Related Issues – Issue #1 – Revision of Bronchial Valve Codes	Request to approve 316X1, 316X1B revised placement codes was approved as CPT Category I codes for bronchial valve placement.	Accepted RUC referral to convert one placement code into two placement codes to parallel the removal codes reviewed at the previous meeting.

CHEST 2012: Destination Atlanta

Think of Atlanta, and you're likely to think of peaches, CNN, Coca-Cola®, *Gone With the Wind,* and southern hospitality. Join your colleagues at CHEST 2012 in Atlanta, a world-class, modern city with a rich, passionate history. Atlanta belies a progressive character that has defined a legacy of civil rights and leadership. Open minds and open arms will welcome you to explore the city's vibrant present and distinguished past.

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Learn what you can do in Atlanta during your free time at CHEST 2012 by visiting atlanta.net.

While at the site, look for:

▶ 50 Fun Things to Do in Atlanta. Discover attractions, historic landmarks, world-class shopping, sporting events, and more.

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▶ What's Hot in Atlanta. Find concerts, theater, art exhibits, athletic events, and more in the events calendar.

▶ Atlanta CityPASS. Use this book of vouchers for six of Atlanta's top attractions for $64. It's a great way to see the city.

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Follow Atlanta on Facebook

"Like" the Atlanta Convention and Visitors Bureau Facebook page to get more tips on what to see and do in Atlanta. facebook.com/visitatlanta.

CHEST 2012 takes place October 20-25. Plan now to attend for essential updates on patient care and practice management strategies. More than 300 general sessions, using a variety of instructional formats, will be presented. Look for hands-on simulation opportunities, case- and problem-based presentations, small-group interactive discussions, self-study opportunities, and more.

Learn more at accpmeeting.org. ■

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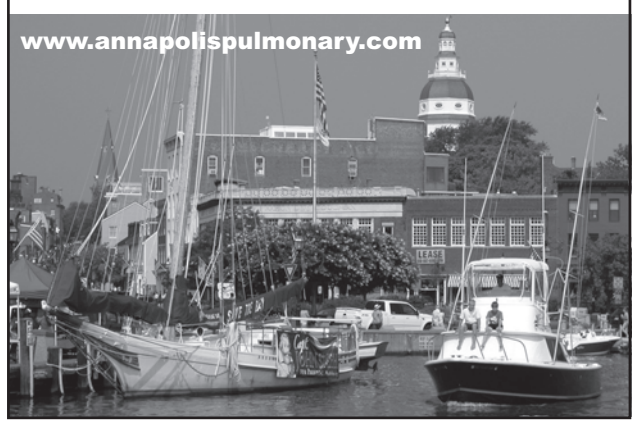

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Hospital Affiliated-Private Practice seeking FT and PT BC/BE Pulmonologist. Successful candidate(s) to join our existing five Physician single- specialty group. We offer a generous mix between office, hospital and a nursing home based practice, we are affiliated with a large university hospital and provide services at local community hospitals as well. Practice includes Directors of a large ventilator unit, critical care, medicine, sleep and pulmonary departments. We are also affiliated with two state of the art sleep labs and rehabilitation centers. We offer a competitive salary, excellent benefits and on call schedule. Our practice offers a balanced lifestyle. Immediate openings are available as well as openings for July 2012. This is not a J-1 visa opportunity. Motivated, qualified candidates should fax CV to 516-796-3205 c/o Cindy Strain or email to: **Cyndy65@aol.com** Call 516-796-3700 for further information on this exciting opportunity.

NEW JERSEY
Director Southern New Jersey Intensivist Program

Director Southern New Jersey Intensivist Program: Seeking BC PCC physician with prior director experience to develop a new intensivist program. Hospital is less than 45 minutes from Philadelphia and is a regional facility serving a population of 350,000. The hospital has a staff of more than 500 physicians and other healthcare providers (including active and courtesy staff). Low-cost housing and farmland make this a nice opportunity for those who like the ocean nearly as well as a big city. Client will not consider contract groups.

Wanda Parker
The HealthField Alliance
866-232-2333, 203-778-3333
healthfield@mindspring.com

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Pulmonary Perspectives

COPDGene Study Generates New Insights Into COPD

In September 2007, the largest study of COPD in the United States was funded by the NHLBI to broadly address unanswered questions about the causes of COPD. The study was funded as paired projects at National Jewish Health in Denver, Colorado, and Brigham and Women's Hospital in Boston, Massachusetts, under the direction of Co-Principal Investigators Dr. James D. Crapo, FCCP; and Dr. Edwin K. Silverman, PhD. The ambitious goals of the project were to enroll 10,000 smokers with and without COPD from two ethnic groups, precisely characterize the subjects using spirometry, respiratory symptoms, medical history, 6-minute walk test, and high-resolution CT scans, followed by genome-wide association testing for susceptibility to COPD and COPD-related traits (Regan et al. *COPD*. 2010;7[1]:32). The extensive clinical, radiographic, and genetic phenotyping would be analyzed to detect novel subtypes of COPD. In addition, the study investigators planned to enhance enrollment of African Americans to address apparent disparities in COPD susceptibility and to potentially discover unique COPD susceptibility genes in this population.

Initially, some skepticism was expressed about the ability to complete enrollment for such a complex project over the 5-year period of funding. Twenty-one clinical centers across the country commenced enrolling subjects in March 2008. Enrollment was completed in just over 3 years due largely to a committed group of investigators and clinical coordinators at each of the sites. CT scans are being analyzed by the Quantitative Imaging Lab at National Jewish, using the VIDA software, for automated measures of emphysema, gas trapping, and airway disease (http://www.vidadiagnostics.com/index.html) and by the Brigham and Women's Hospital imaging team using an alternative software package (http://www.slicer.org). A separate project to maintain longitudinal contacts was established, and 80% of the cohort has been reporting ongoing health data approximately every 6 months.

More than 30 scientific papers are either published or in preparation with early results from the study. These include a number of genetics papers in which COPDGene GWAS data from an early group of 1,000 subjects was used in combination with other large cohorts to identify or confirm genetic findings, such as associations to FAM13A for COPD affection status (Cho et al. *Nat Genet*. 2010;42[3]:200), FTO variants to BMI in COPD subjects (Wan et al. *Am J Res Cell Mol Biol*. 2011;45[2]:304), and smoking behaviors to regions of CYP2A6 and a locus at chromosome 15q25 (Siedlinski et al. *Thorax*. 2011;66[10]:894).

Interstitial lung disease in the context of smoking was the topic of another study from COPDGene (Washko et al. *N Engl J Med*. 2011; 364[10]:897). Using visual reads of the CT scans from 2,416 subjects enrolled in COPDGene, the group found 194 subjects (8%) had evidence of interstitial lung abnormalities (ILA). These subjects with CT evidence of ILA had greater smoking exposure, were more current smokers, had lower total lung capacity, and were more likely to fall into the unclassified category of subjects. However, there was a definite overlap of ILA with COPD—63 (32%) of the ILA subjects fell in the GOLD 2-4 group, and these subjects showed less emphysema and lower total lung capacity than subjects without ILA.

A unique group of smokers has emerged from the COPDGene project that is not classified by GOLD criteria but shows significant health effects. These subjects have a normal (>0.7) FEV_1/FVC ratio but reduced (<80% predicted) FEV_1. They have been termed GOLD unclassified subjects. Early in the recruitment process for COPDGene, it was decided that the study would encompass all smokers with the specified smoking exposure and not exclude subjects who failed to meet the current classification criteria for COPD. The rationale for this was that these subjects had smoking exposure and either represented an alternative control group or potentially a group "at risk" of smoking-related disease.

For purposes of studying genetic associations to COPD, this group represents an important comparison group. The GOLD unclassified subjects constituted 9% of the subjects in COPDGene study (Wan et al. *Am J Respir Crit Care Med*. 2011;184[1]:57). They showed greater impairment of the 6-min walk, fewer pack-years of smoking, higher BMI, reduced total lung capacity, more comorbid cardiovascular disease, and lower oxygen saturation. The unclassified group is heterogeneous, with about half of the group having a reduced total lung capacity, slightly more than half of the group is obese with BMI>30, and the group overall has significantly more comorbid disease and worse physical function than the GOLD 1 group. Further study will be done on this group of smokers as the full cohort is analyzed and genetic data become available.

Several groups of investigators have used the early COPDGene data to look at the unique aspects of race and COPD. Using the large population of African American subjects enrolled in the study, investigators found significant differences in quality of life and function (Han et al. *Chest*. 2011; 140[5]:1169). Although African American subjects had similar mean percent predicted FEV_1 values compared with non-Hispanic white subjects, they had fewer pack years of smoking exposure and worse 6-minute walk distance (381 meters ±135 vs 298 meters ± 119, P <.001).

Within COPD subjects who reported exacerbations, African Americans had worse quality of life and more dyspnea.

Another study that addressed differential impacts of race looked at Early Onset COPD (Foreman et al. *Am J Respir Crit Care Med*. 2011; 184[4]:414). In this study, the authors found that severe early onset COPD (age < 55 years and FEV_1< 50% predicted) was identified more often in African American subjects (present in 42% of African Americans compared with 14% of the non-Hispanic white group, P <.0001). Women were also overrepresented in the early onset group, and both maternal smoking and maternal history of COPD were significant predictors of early disease.

Chronic bronchitis as a distinct phenotype in COPD was identified by another group (Kim et al. *Chest*. 2011;140[3]:626). Chronic bronchitis was defined as cough and phlegm production for greater than 3 months, and 27% of the subjects with COPD studied fell into that category. These subjects were younger, had greater pack-years of exposure, were more likely to be current smokers, had more exacerbations, and were more likely to have severe exacerbations than subjects without chronic bronchitis, although their mean FEV_1 was the same, and there was no difference in percent emphysema or gas trapping. The subjects with chronic bronchitis did have evidence of greater airway disease with mean segmental wall area percent significantly greater. This group is posited to need directed therapy for reducing smoking and airway mucin production.

The COPDGene study is poised to provide important information about both genetic causes of COPD and the natural history of the disease in the coming years. The investigators hope to obtain additional funding to perform a second evaluation of these subjects in order to determine disease progression over time. The genetic data from the whole cohort are in preparation for analysis. With data on 10,000 well-characterized smokers, we anticipate detecting additional important genetic findings over the next few years that, hopefully, will offer opportunities to improve treatment or reduce the incidence of this disabling disease. ■

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Guest Editor's Note

The COPDGene project offers an incredible degree of promise in our efforts to better understand the disease we call "COPD." The project is already starting to nicely demonstrate that COPD is not merely one homogeneous disease but rather multiple different diseases with some commonality in their presentation. The early data from COPDGene are pointing us in that direction, with evidence supporting some specific phenotypes, such as the restrictive or "unclassified" group, the early-onset group, and the chronic bronchitis group. Additional work will, in all likelihood, identify additional important subgroups, along with genetic or other markers of disease activity and severity. The ultimate goal of this work and other related projects around the world is to prevent, treat, and even cure COPD.

We have come a long way over the last 5 years, but still have a long way to go toward our goal of decreasing the morbidity and mortality of this group of diseases.

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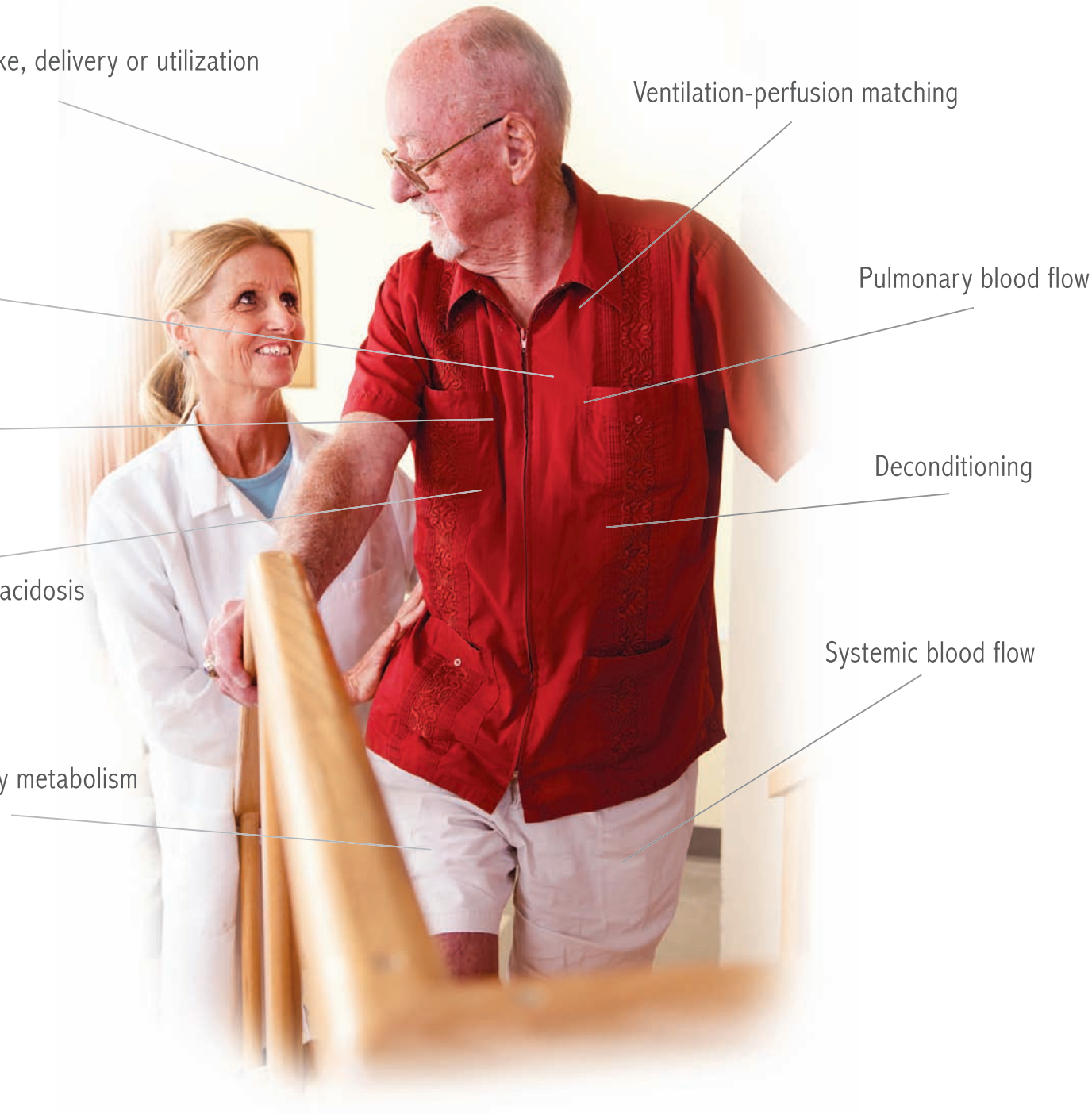

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