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The BADGER trial examined the best next step for children whose asthma is not controlled on low-dose corticosteroids.

Step-Up Tx Helped Tame Kids' Asthma

BY HEIDI SPLETE
Elsevier Global Medical News

NEW ORLEANS — Approximately 98% of children with uncontrolled asthma experienced clinically significant improvements on each of three types of step-up therapy, but treatment with long-acting beta-agonists yielded significantly better responses, according to a new study.

"Step-up with long-acting beta-agonists was more than one and a half times more likely to produce the best response," Dr. Robert F. Lemanske Jr. said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. The results were presented at the meeting and published online in the New England Journal of Medicine.

Asthma treatment with long-acting beta-agonists (LABAs) has come under scrutiny in the wake of recent recommendations from the Food and Drug Administration to step down the use of these drugs in asthmatic children once their asthma is controlled. But few data are available to guide clinicians on the next steps in the treatment of children with asthma who are already using a low-dose inhaled corticosteroid (ICS), Dr. Lemanske said.

To determine whether there is a best next step for children whose asthma is not controlled on low-dose corticosteroids, Dr. Lemanske of the University of Wisconsin, Madison, and his colleagues developed the Best Add-on Therapy Giving Effective Responses (BADGER) trial (N. Engl. J. Med. 2010;362:975-85).

"This trial was not intended to look at safety," Dr. Lemanske emphasized.

In the study, the researchers randomized 182 children aged 6-17 years with uncontrolled mild to moderate asthma to one of three therapies in three 16-week study periods. Every patient received each of the three therapies for 16 weeks. The first 4 weeks of the last two 16-week periods were considered run-in and washout periods. A total of 25 treatment failures occurred,

See **Asthma** • *page 2*

NCCN Releases First Guidelines For Mesothelioma

Will assist in making difficult diagnosis.

BY PATRICE WENDLING
Elsevier Global Medical News

HOLLYWOOD, FLA. — A pleural biopsy should be combined with cytology and chest CT to make the diagnosis of mesothelioma, according to the first guidelines published on this rare cancer by the National Comprehensive Cancer Network.

About 2,000 cases of malignant pleural mesothelioma—typically occurring as a result of asbestos exposure—are diagnosed in the United States each year. Case studies have also suggested a link between radiation exposure for Hodgkin's disease and the subsequent development of malignant mesothelioma.

The diagnosis of malignant pleural mesothelioma is difficult, and is often missed on pleural fluid cytology alone, said Dr. Lee M. Krug, who presented the guidelines at the National Comprehensive Cancer Network's annual conference.

Patients with mesothelioma typically present with recurrent pleural effusion and/or pleural thickening. Thus, the disease can be confused with mesothelial hyperplasia, fibrous pleurisy, adenocarcinoma, sarcoma, and metastases.

The initial work-up should include chest CT with contrast; thoracentesis for cytologic assessment; and pleural biopsy (preferably a video-assisted thoracoscopic surgery biopsy). Talc pleurodesis or pleural catheter may be required for the management of pleural effusion.

Data are emerging on the use of possible serum markers for mesothelioma, but such markers are not ready for "prime time" as diagnostic

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Stereotactic Radiation Controlled Tumors

BY MARY ANN MOON
Elsevier Global Medical News

Stereotactic body radiation therapy yielded a 97.6% rate of primary tumor control at 3 years in a clinical trial of inoperable early-stage lung cancer.

That control rate is more than double that achieved with conventional radiotherapy, Dr. Robert Timmerman of the University of Texas Southwestern Medical Center, Dallas, and his associates reported in the March 17 issue of JAMA.

"Primary tumor control is an essential requirement for the cure of lung cancer. Treatments applied for curative intent must be judged at least partly on their ability to control gross disease," the investigators said.

Stereotactic body radiation therapy (SBRT) is a noninvasive approach restricted to extracranial sites in which many "small, highly focused, and accurate radiation beams" deliver potent doses to tumor targets during one to five sessions over the course of 2 weeks. Dr. Timmerman and his colleagues performed what they

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Step-Up Therapies Compared

Asthma • *from page 1*

and complete data were available for 157 patients.

The three therapies were ICS step-up therapy, consisting of 250 mcg of fluticasone twice daily; LABA step-up therapy, consisting of 100 mcg of fluticasone plus 50 mcg of salmeterol twice daily; or leukotriene-receptor antagonist therapy (LTRA), consisting of 100 mcg of fluticasone twice daily plus an age-appropriate dose (5 or 10 mg) of montelukast daily.

In pair comparisons, the proportion of children who responded best to LABA was 52% vs. LTRA (34%), and 54% vs. ICS (32%). The differences between LABA and each of the other two protocols were significant, but the differences between LTRA and ICS were not.

Of several factors used to predict best response, only a higher baseline score (greater than 19) on the Asthma Control Test or Childhood Asthma Control Test (depending on age) was a significant predictor of best response to LABA therapy.

The findings suggest a ceiling effect beyond which low-dose ICS therapy is not effective, the researchers wrote.

Although the proportion of children who had a best response to LABA was significantly greater than with the other two treatments, "many children demonstrated a best response to either ICS or LTRA step-up therapy, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy," Dr. Lemanske said at the meeting.

When the results of one of the three treatment plans—LABA, LTRA, or step-up ICS—are unsatisfactory, "what you should not do is go to step 4," Dr. Lemanske said. Instead, "based on the fact that our data showed a differential response to one of these three options in almost all of the kids in the trial, we would suggest that you choose one of the other options at step 3 care," he said.

A total of seven serious adverse events were reported. The most common serious adverse event was asthma exacerbation.

The findings inform clinical practice, wrote Dr. Erika von Mutius of the University Children's Hospital in Munich and Dr. Jeffrey M. Drazen, FCCP, editor-in-chief of the New England Journal of Medicine, in an editorial.

"Since any of the three step-up therapies may work in an individual patient, we would base our first choice for a given patient on three things: surety of safety, price, and convenience, in that order," they wrote.

Given the safety concerns regarding LABAs, the doctors wrote, their first choice would be ICS or LTRA (N. Engl. J. Med. 2010;362:1042-3).

Dr. Lemanske has received consulting fees and grant support from multiple pharmaceutical companies, including MAP Pharmaceuticals Inc., Gray Consulting Inc., Merck & Co., AstraZeneca, and Genentech Inc. The study was funded in part by the National Heart, Lung, and Blood Institute, and the study drugs and placebos were supplied by GlaxoSmithKline and Merck. ■

COLLEAGUE COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Among the subgroup analyses, ethnic differences are particularly interesting. African Americans had equal results stepping up by increasing the dosage of inhaled corticosteroids, compared with adding a LABA. This is also the ethnic group in which there have been the most safety concerns about LABA use. Further directed study in this population seems warranted to determine the mechanisms of these actions.

Primary-Site Recurrence Low

Stereotactic • *from page 1*

described as the first North American multicenter study of that technique in 55 patients with medically inoperable early-stage non–small cell lung cancer.

Patients were enrolled in the study between May 2004 and October 2006. They were followed for a median of 34 months (range 5-50 months); 29 patients were still alive at press time. Twenty-eight patients showed a complete response to therapy, and 21 showed a partial response, for a combined 89% response rate.

Only one patient showed a documented recurrence at the primary site, and there were no marginal recurrences. Thus, the 3-year primary tumor control rate was 97.6%.

That is more than twice the rate of primary tumor control reported previously with conventional radiotherapy, Dr. Timmerman and his colleagues said (JAMA 2010;303:1070-6).

"The most disappointing finding in this trial was the rate of disseminated recurrence (22% at 3 years)," the investigators noted.

Three patients developed recurrences in the involved lobe of the lung, 2 developed regional recurrences, and 11 developed disseminated recurrences. A total of 26 patients died during follow-up, 10 of them from lung cancer.

Seven patients experienced grade 3 adverse events related to treatment, and two experienced grade 4 adverse events. An additional six patients developed adverse events that were ascribed to SBRT, even though they had not been classified prospectively as such.

The study was funded by grants from the National Cancer Institute and the Advanced Technology Consortium. Dr. Timmerman reported receiving research grants for technology development from Varian Medical Systems Inc. and Elekta Oncology AB; both companies manufacture equipment used in SBRT. Dr. Timmerman also reported receiving grants from the National Institutes of Health and the Department of Defense for separate studies of stereotactic radiotherapy. ■

COMMENTARY

W. Michael Alberts, FCCP, comments: SBRT, as a radiation therapy delivery technique, appears to be an excellent treatment modality for patients unable or unwilling to undergo resectional surgery. A 97.6% primary tumor control seems almost too good to be true.

I wonder how SBRT might fare when compared to surgery in operable "early-stage" lung cancer.

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CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group and Elsevier Global Medical News. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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FDA Advisory Panel Backs Drug for Treating IPF

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

SILVER SPRING, MD. — The majority of a Food and Drug Administration advisory panel recommended that pirfenidone be approved as a treatment for patients with idiopathic pulmonary fibrosis.

At a meeting of the FDA's Pulmonary-Allergy Drugs Advisory Committee, the panel voted 9-3 to recommend approval for the proposed indication: reduction in the decline of lung function in idiopathic pulmonary fibrosis (IPF). Those voting in favor of approval agreed that the data on the drug showed treatment was beneficial in slowing the progression of the disease.The FDA usually follows the recommendations of its advisory panels.

Panelists said, however, that more data are needed to help identify which subsets of patients with IPF may benefit most from treatment and recommended that safety of the drug should be monitored long term, possibly in a patient registry.

There is no FDA-approved treatment for IPF, a progressive, irreversible diffuse parenchymal lung disease of unknown etiology that is typically diagnosed after age 50. Approximately 100,000 people in the United States have the disease, according to pirfenidone's manufacturer, InterMune.

Pirfenidone, an orally administered drug with an unknown etiology of action, has exhibited anti-inflammatory and antifibrotic properties in animal and in vitro studies, according to InterMune. The proposed daily dose is 2,403 mg, taken in three divided doses in a capsule formulation.

Pirfenidone was compared to placebo in two phase III studies comparing pirfenidone to placebo in almost 800 patients aged 40-80 years (mean age was 67-68 years), with a clinical, radiographic, and/or pathologic diagnosis of IPF. The primary end point was the change in the percent predicted forced vital capacity (FVC) from baseline to week 72, which was statistically significant in one of the two studies.

In one study, 20% of those treated with 2,403 mg of pirfenidone a day had at least a 10% decline in percent predicted FVC at week 72, compared with 35% of those on placebo, a statistically significant difference. There was no decline in percent predicted FVC at week 72 in 24% of those on the 2,403-mg dosage, compared with 14% of those on placebo, also a statistically significant difference. Progression-free survival, a secondary end point, also favored pirfenidone.

But in the other study, there was no significant difference in the percent predicted FVC change among patients treated with 2,403 mg/day of pirfenidone and those on placebo at 72 weeks, although the differences were significant in favor of pirfenidone at week 48.

Nausea and other gastrointestinal side effects and photosensitivity reactions were more common among those treated with pirfenidone. A total of 14 patients in both studies had liver enzyme elevations, which were reversible and managed by modifying the dose, according to InterMune, which has proposed a risk management plan for prescribing the drug that would minimize the potential risk of hepatotoxicity and photosensitivity reactions. ■

COLLEAGUE COMMENTARY

Dr. Joseph Barney, FCCP, comments: This is a timely and important article for pulmonologists and physicians treating patients with pulmonary fibrosis. We participated in one of these phase III studies at the University of Alabama at Birmingham, for pirfenidone, so I have some experience with this protocol in our interstitial lung disease program. I think this medication, while somewhat controversial in its net contribution to pulmonary fibrosis, has shown promise in slowing progression of loss of lung function in a terribly disabling disease. It potentially opens the door for streamlining the process of development and approval of subsequent therapies for pulmonary fibrosis. Pirfenidone is neither a cure nor a magic bullet for patients with IPF, but it does seem to offer hope for delaying progression, which may afford patients on transplant lists more time to wait for vital organs to become available.

FDA Approves Orphan Drug For Cystic Fibrosis

BY LAUREN SMITH
"The Pink Sheet"

The Food and Drug Administration has approved Cayston to improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*, a therapeutic area with few meaningful therapies.

The Feb. 22 approval comes as no surprise, as the orphan drug was seen as an urgently needed therapeutic to treat the respiratory and pulmonary symptoms of CF, and led the FDA's Anti-Infective Drugs Advisory Committee to overwhelmingly support approval of Cayston (aztreonam for inhalation solution). The drug is manufactured by Gilead Sciences.

Members of the committee said the bar for approval should be set "quite low" due to the lack of meaningful alternatives, despite both the FDA and the panelists' misgivings about missing data and negative regimen effects in the two pivotal trials.

The approval was lauded by the Cystic Fibrosis Foundation, whose president and CEO Robert Beall said in Gilead's press release, "As the first new inhaled antibiotic approved for use in cystic fibrosis in more than a decade, Cayston therefore represents an important therapeutic option in the care of patients with cystic fibrosis."

The foundation is also working with Gilead's marketing team to establish the Cayston Access Program, a call center developed with the Cystic Fibrosis Foundation Pharmacy (a wholly owned subsidiary of the Cystic Fibrosis Foundation), which will assist people with cystic fibrosis and members of their care team with insurance verification, referral to participating specialty pharmacies, claims support, and co-pay assistance.

Gilead is also establishing a program designed to minimize barriers to access for Cayston for uninsured, privately insured, and government-insured people.

The drug will be available in the United States through certain specialty pharmacies. Cayston, administered at a dose of 75 mg three times daily over a 28-day period, is delivered via the Altera Nebulizer System, a portable, drug-specific delivery device developed by PARI Pharma.

Cayston was approved in the European Union and Canada in September 2009 and was approved in Australia in January 2010. Applications for marketing are currently pending in Switzerland and Turkey.

Elsevier publishes *"The Pink Sheet"* and Elsevier Global Medical News. ■

COMMENTARY

Dr. Philip Marcus, MPH, FCCP, comments: New drugs for diseases that do not have broad appeal in terms of marketability are always welcomed by the populations in need. This represents a significant advance for patients with cystic fibrosis colonized and infected with *P. aeruginosa*, as a step before systemic antibiotic therapy.

Combo Therapies Were Tops In Smoking Cessation

BY HILLEL KUTTLER
Elsevier Global Medical News

BALTIMORE — Utilizing a nicotine patch or bupropion together with a nicotine lozenge was the most effective of five therapies tested for promoting smoking abstinence and avoiding a lapse or relapse into smoking, according to a prospective study of 1,504 smokers.

All five therapies were "significantly better than placebo in promoting initial abstinence," Sandra Japuntich, Ph.D., reported at the annual meeting of the Society for Research on Nicotine and Tobacco.

LAPSING AND RELAPSING MAY BE AN INDICATION THAT THE MEDICATION ISN'T WORKING, AND THAT PATIENTS MIGHT NEED TO TRY SOMETHING ELSE.

The therapies also were effective at preventing relapse, said Dr. Japuntich, a postdoctoral fellow at Massachusetts General Hospital's Mongan Institute for Health Policy, Boston.

The placebo-controlled trial sought to identify the effects on smoking cessation milestones of five pharmacologic therapies: nicotine lozenge, nicotine patch, bupropion, bupropion with a nicotine lozenge, and nicotine patch with a nicotine lozenge.

The milestones were one period of 24-hour abstinence within 2 weeks of a target quit date, lapsing with at least one cigarette, and relapsing into regular smoking for at least 7 consecutive days.

A total of 70% of smokers on placebo initially abstained, compared with 92% of those using a nicotine patch with a nicotine lozenge, 86% on bupropion with a lozenge, 81% on bupropion, 81% on a lozenge, and 88% on a nicotine patch.

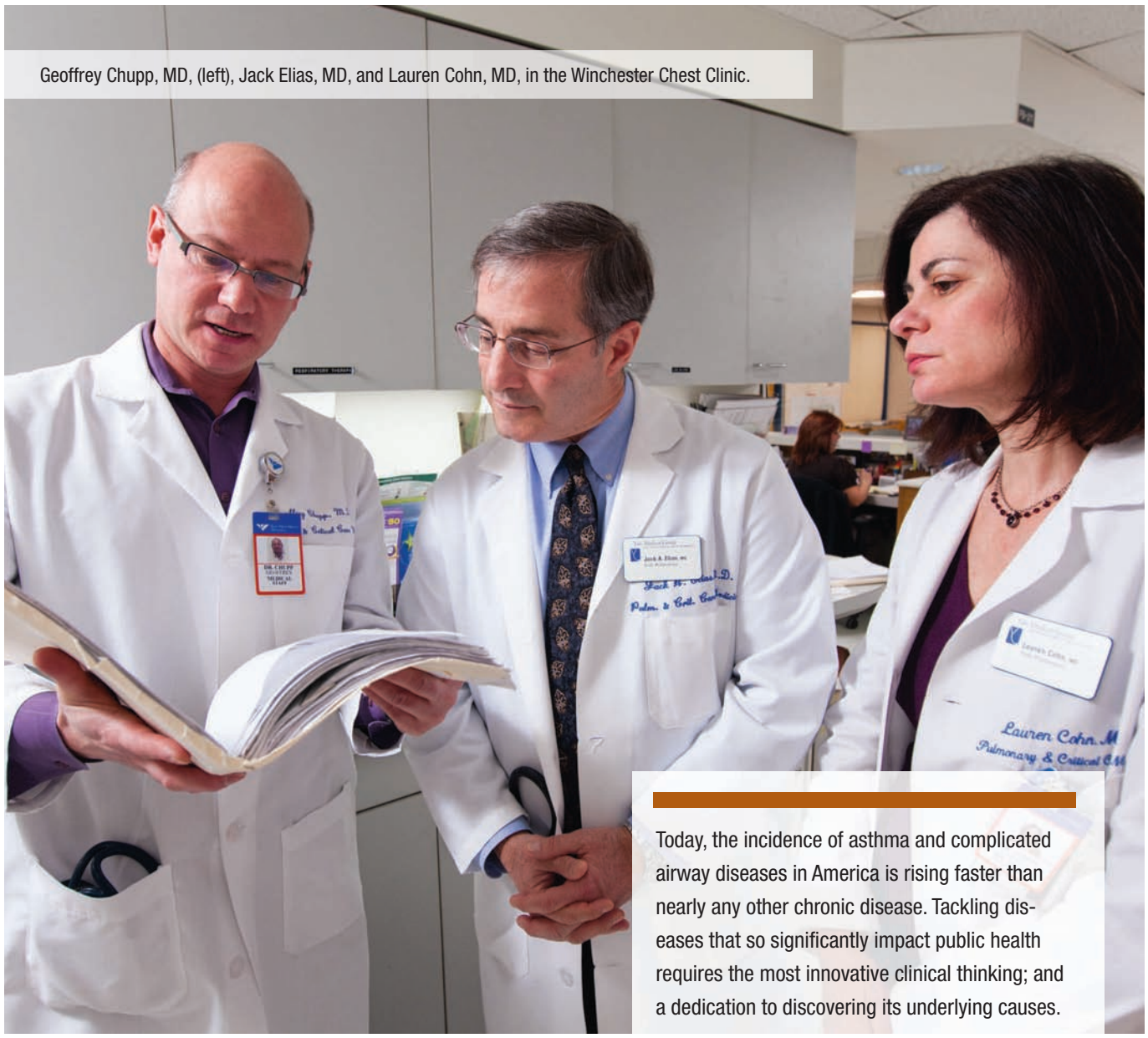
Among those who initially abstained, 83% on placebo lapsed, compared with 70% of smokers who used a nicotine patch with a lozenge, 71% on bupropion with a lozenge, 74% on bupropion, 73% on a lozenge, and 76% on a patch.

Of those who lapsed, 69% on placebo relapsed, compared with 61% using a nicotine patch, 64% on bupropion with a lozenge, 63% on bupropion, 62% on a lozenge, and 61% on a patch with a lozenge.

"According to our study, the strongest treatment effects are happening in the first week or two," she said. "We should know whether medication is working [by then]. If you get past the first week or two on medication and you haven't lapsed, then the medication is working."

On the other hand, for those who do not stay abstinent, "it could be that lapsing and relapsing is an indication that the medication isn't working, and that the patients might need to try something else," she said.

Dr. Japuntich had no conflicts of interest to report. One of her coinvestigators, Timothy B. Baker, Ph.D., has served on research projects sponsored by pharmaceutical companies including Pfizer Inc., Glaxo Wellcome Inc., Sanofi Inc., and Nabi Pharmaceuticals Inc. ■



Geoffrey Chupp, MD, (left), Jack Elias, MD, and Lauren Cohn, MD, in the Winchester Chest Clinic.

Study Links Asthma, Lack Of Vitamin D

BY HEIDI SPLETE
Elsevier Global Medical News

NEW ORLEANS — Approximately half of children with asthma were deficient in vitamin D in a study of 99 children aged 18 and younger. The findings were presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Previous studies have indicated that vitamin D insufficiency contributes to the pathophysiology of allergic disease, but data on vitamin D's impact on children with allergies and asthma are limited, said Dr. Daniel Searing of National Jewish Health in Denver.

In this study, Dr. Searing and colleagues identified 99 children who had asthma, atopic dermatitis, and/or a food allergy. The researchers assessed vitamin D by measuring serum 25-hydroxyvitamin D levels. Overall, 47% of the patients had insufficient levels of vitamin D (less than 30 ng/mL). The median vitamin D level was 31 ng/mL.

To assess the impact of vitamin D on inflammation, the researchers cultured peripheral blood mononuclear cells (PBMC) from 11 patients using either 10 nM vitamin D or a placebo medium for 24 hours, and supplemented them with either 10 or 100 nM of dexamethasone for the last 3 hours of culturing. Next, they measured mitogen-activated protein kinase phosphatase-1 (MKP-1) and interleukin-10 (IL-10.)

"Vitamin D enhances glucocorticoid induction of MKP-1 and IL-10 in asthmatic PBMC in vitro," the researchers wrote. Vitamin D addition can enhance the activity of dexamethasone more than 10-fold, they added.

"The relationship between vitamin D and corticosteroid pathways, as well as its effect on the inflammatory response, is not fully understood," the researchers emphasized. But the results suggest that vitamin D supplementation may enhance the anti-inflammatory function of corticosteroids in asthma patients, they noted.

Median vitamin D levels were significantly lower in children taking inhaled corticosteroids (29 ng/mL), oral corticosteroids (25 ng/mL), and long-acting beta-agonists (25 ng/mL), compared with children who were not taking inhaled corticosteroids, oral corticosteroids, or long-acting beta-agonists (35 ng/mL, 32 ng/mL, and 34 ng/mL, respectively). In addition, median vitamin D levels were significantly lower in children with positive vs. negative aeroallergen sensitivity to dog dander (29 ng/mL vs. 35 ng/mL).

Dr. Searing had no financial conflicts to disclose. The study was supported in part by a grant from the National Institutes of Health. ■

Protocols Put Inpatient Glucose Targets Into Practice

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO — Meeting the targets in consensus recommendations on inpatient glycemic control requires different protocols for different kinds of patients.

For hospitalized patients who are not critically ill, a protocol employing scheduled subcutaneous insulin therapy with basal, nutritional, and correctional components is effective, Dr. Mary T. Korytkowski said. For critically ill inpatients, intravenous insulin infusion protocols are better for achieving and maintaining glycemic control, she said at a meeting sponsored by the American Diabetes Association.

Use of prolonged therapy with 'sliding scale' insulin alone is not recommended.

DR. KORYTKOWSKI

Many hospitals further subdivide the protocol for critically ill patients to have different glycemic targets for surgical and nonsurgical ICU patients, added Dr. Korytkowski, professor of medicine at the University of Pittsburgh's Center for Diabetes and Endocrinology.

A 2009 consensus statement from the American Association of Clinical Endocrinologists and the American Diabetes Association recommended maintaining glucose levels between 140 and 180 mg/dL in most critically ill patients, but added that glucose levels of 110-140 mg/dL may be appropriate in some, such as those in cardiothoracic intensive care.

"We don't have the data to prove that outside the surgical intensive care studies," she said, "so many hospitals now have two protocols—one for their surgical patients, and one for nonsurgical patients."

In noncritically ill inpatients, the consensus statement recommends targeting premeal glucose levels of 100-140 mg/dL and random glucose test results below 180 mg/dL (Endocr. Pract. 2009;15:353-69 and Diabetes Care 2009; 32:1119-31).

Prolonged therapy with "sliding scale" insulin alone is not recommended, Dr. Korytkowski stressed. "This whole idea of putting patients on sliding scale insulin and continuing it for the duration of their hospitalization independent of what their blood sugar levels are needs to be stopped," she said.

The 2009 consensus recommendations steered clinicians away from aiming for lower glucose levels of 80-110 mg/dL in hospitalized patients to reduce risk for complications related to uncontrolled hyperglycemia while also minimizing risk for sever hypoglycemia.

Institutions can choose from a number of published protocols for managing inpatient glucose levels to meet the consensus recommendations, she said. For critically ill patients, it's better to initiate insulin infusions when their glucose levels reach the lower end of the 140- to 180-mg/dL range rather than wait for levels to climb above 180 mg/dL, she suggested.

Her institution initiates insulin therapy by obtaining or estimating the patient's weight in kilograms, then calculating the total daily dose of insulin as 0.2-0.4 units/kg per day. Clinicians then choose the dosing schedule, usually giving 50%-60% of the total daily dose as basal insulin, with the remainder as premeal or nutritional bolus insulin divided up in three or four doses. Correction insulin is given when blood glucose levels exceed the goal range.

"This is not a one-stop process," Dr. Korytkowski said. Each day, the glucose levels are evaluated and the insulin regimen is adjusted to avoid both hyper- and hypoglycemia.

The basal-bolus insulin protocol was shown to be safe when compared with sliding-scale insulin in a prospective, randomized, controlled trial of 130 inpatients with type 2 diabetes, she noted (Diabetes Care 2007;30:2181-6).

Dr. Korytkowski also recommends monitoring glucose for at least 48 hours in all hospitalized patients who are starting glucocorticoid therapy or enteral or parenteral nutrition, because these are associated with increased risk for hyperglycemia. Prescribe insulin therapy as needed in these patients based on bedside blood glucose monitoring, and be proactive about adjusting insulin therapy especially during initiation and tapering of steroid therapy, she advised.

"One thing that's very important when patients go home and their steroid doses are tapered is that they need to know how to taper their insulin along with tapering their steroid, so they don't come back in 2-3 weeks in a hyperglycemic event," she said.

Dr. Korytkowski and her associates published a glycemic management algorithm for patients receiving enteral nutrition that was shown to be safe in a prospective, randomized trial in 50 inpatients (Diabetes Care 2009;32:594-6).

Establishing a formal protocol for patients who enter the hospital on insulin pumps also can reduce confusion and treatment variability, she added. At her institution, patients who used insulin pumps before entering the hospital can continue to use them as inpatients provided that they have the mental and physical capacity to do so. Ideally, hospital staff who have experience in insulin pumps should be available if needed.

Dr. Korytkowski said she has no conflicts of interest to disclose. ■

Intensive Insulin Failed to Improve Mortality in Septic Shock

BY MARY ANN MOON
Elsevier Global Medical News

Compared with usual care, intensive insulin therapy failed to improve in-hospital mortality in a large clinical trial of adults receiving hydrocortisone for septic shock, according to a report in the Jan. 27 issue of JAMA.

The study results do little to clarify the controversial issue of insulin therapy in such patients, and in fact muddy the waters even further, according to Dr. Greet Van den Berghe. The trial investigators "executed a difficult multicenter trial in very complex, seriously ill patients, and yet clinicians can only conclude from their efforts that there is still uncertainty about how to do things differently," she wrote in an accompanying editorial.

Severe sepsis often induces hyperglycemia, and the routine use of corticosteroids to reverse septic shock often aggravates the hyperglycemia. Insulin therapy to reduce blood glucose has been widely adopted in ICUs worldwide and incorporated into treatment guidelines for patients receiving corticosteroids for septic shock.

The question of how intense such insulin therapy should be is still debated. Dr. Djillali Annane and his associates in the Corticosteroids and Intensive Insulin Therapy for Septic Shock (COIITSS) trial compared the usual practice of using insulin therapy to target blood glucose levels to 150 mg/dL with the more intensive approach of aiming for 80-110 mg/dL.

The open-label trial involved 509 patients treated at 11 ICUs in France for severe sepsis and multiple organ dysfunction requiring intravenous hydrocortisone. Patients were randomly assigned to receive intensive insulin and hydrocortisone, intensive insulin and hydrocortisone plus fludrocortisone, conventional insulin and hydrocortisone, or conventional insulin and hydrocortisone plus fludrocortisone.

A secondary objective of the study was to determine whether adding fludrocortisone to the treatment regimen would improve outcomes. Fludrocortisone did not interact with insulin or affect the primary objective of the trial, and it was found not to improve patient outcomes.

Participants were followed for 6 months. Patients receiving intensive insulin therapy "had markedly lower blood glucose from the first day through their last day in the ICU than those in the control group," wrote Dr. Annane of the University of Versailles, Garches, France, and his associates.

The primary outcome measure—in-hospital or 90-day mortality, whichever came first—was not significantly different between the intensive-insulin (46%) and the usual-insulin (43%) groups.

None of the secondary outcomes differed among the groups either. Secondary outcomes measures included time to improvement of organ failure, ICU length of stay, hospital length of stay, rate and severity of serious adverse events, and the occurrence of superinfection.

These study results provide "no evidence to support a strategy of intensive insulin therapy aimed at maintaining blood glucose levels in the range of 80-110 mg/dL," Dr. Annane and his associates concluded (JAMA 2010;303:341-8).

In her editorial, Dr. Van den Berghe of the Catholic University of Leuven (Belgium) noted that, despite the different targets for blood glucose between the study groups, the actual blood glucose levels achieved overlapped considerably. "Thus, the lack of difference in outcome could be because … the actual blood glucose levels were not substantially different," she noted.

Dr. Van den Berghe also took issue with the researchers' assessment of the statistical power of the COITTSS trial.

"The 509 patients studied in the COIITSS trial are not sufficient to confidently conclude equivalence between the 2 compared blood glucose targets. Thus, clinicians … will still be left with uncertainty as to whether insulin should be given and to what level the blood glucose should be lowered, adding to the uncertainty of whether to treat with hydrocortisone in the first place," she wrote (JAMA 2010;303:365-6).

The COIITSS trial was sponsored by the Assistance Publique-Hôpitaux de Paris. Dr. Annane and associates reported no conflicts of interest. Dr. Van den Berghe reported receiving research funding from the Methusalem program, which is sponsored by the Flemish government. ■

COLLEAGUE COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: This report describes yet another study of the use of intensive insulin therapy in a population of critically ill patients with septic shock. This multicenter trial in France showed no mortality benefit. The study set a higher glucose target than prior trials to lessen likelihood of hypoglycemia. The significant overlap of actual measured glucose values between groups potentially impacted the mortality difference. This issue, combined with the relatively small number of patients in the four treatment arms, resulted in an overall inability to help address the difficult questions posed. We look forward to more information on this controversial and important issue in our critically ill patients.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WBC:18.1
MRSA
nosocomial pneumonia
PMNs:80%,bands:15%
creatinine:2.6
CXR:LLL infiltrate

Some patients have ZYVOX written all over them

With proven efficacy, excellent tissue penetration, and clear and consistent dosing, count on ZYVOX to treat MRSA* in patients with nosocomial pneumonia whose conditions are complicated by renal insufficiency.[1-3]

— Please see www.zyvox.com for further information

IV/Oral
ZYVOX®
(linezolid)

CONFIDENCE TO FACE COMPLEXITY

ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

ZYVOX use is contraindicated in patients with known hypersensitivity to linezolid or any of the other product components.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following: directly and indirectly acting sympathomimetic, vasopressive, and dopaminergic agents.

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine, or buspirone.

Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis.

Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.

Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.

Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG; and Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32(3):402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH; for Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25(3):980-992. **3.** Boselli E, Breilh D, Rimmelé T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med*. 2005;33(7):1529-1533.

Please see brief summary on adjacent pages.

No-Sedation Approach Helped Ventilated ICU Patients

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

Critically ill, mechanically ventilated medical and surgical patients who were not sedated while in an intensive care unit spent significantly less time in the unit and in the hospital, and less time on a ventilator, than were those who were sedated with daily interruptions, the standard protocol for most hospitals, according to a randomized Danish study.

"Results from this single-centre study suggest that a strategy of no sedation is promising, but a multicentre trial is needed to show that the benefits of this strategy can be reproduced in other facilities," Dr. Thomas Strøm of the departments of anesthesia and intensive care medicine, Odense (Denmark) University Hospital and his associates reported in the February issue of the Lancet.

The hospital has used a no-sedation approach for mechanically ventilated patients in the ICU since 1999, using IV bolus doses of morphine but no sedatives or analgesics.

In response to calls in editorials and articles to conduct randomized trials aimed at reducing the use of sedation, the investigators conducted a prospective, unblinded study of critically ill adults (mean age 65-67 years), who were expected to need mechanical ventilation for more than 24 hours. They were randomized to receive either no sedation or sedation with 20 mg/mL of propofol for 48 hours, followed by 1 mg/mL of midazolam with daily interruptions, until waking. The APACHE II scores were 26 for both groups. Both groups were treated with bolus doses of morphine. The researchers enrolled 140 patients, but 27 were eliminated because they died or

were extubated within 48 hours (Lancet 2009;375:475-80).

The primary end point was the number of days spent without mechanical ventilation, which was significantly different between the two groups: The 55 remaining patients in the no sedation group spent a mean of 13 days without mechanical ventilation, compared with 9.6 days among the 58 remaining patients in the sedation group. The no sedation patients spent a mean of 13.1 days in the ICU, versus 22.8 days for the sedation group, also a significant difference. Hospital stays also were significantly shorter among those who were not sedated: a mean of 34 days, versus 58 days among those who were sedated.

Secondary end points—accidental extubation, the need for CT or MRI brain scans, or ventilator-associated pneumonia—were not different between the two groups. However, 20% of those in the no-sedation group exhibited episodes of "agitated delirium," compared with 7% of those in the sedation group, a significant difference.

There were also fewer deaths in the ICU in the no-sedation group: 12 (22%) of the 55 patients died in the ICU, compared with 22 (38%) of those in the sedation group, a nonsignificant difference.

The limitations of the study included the fact that it was conducted at a single hospital and was unblinded. And because the ICU has one nurse for every patient, as well as an extra person on the unit to help calm patients, the results may not be generalizable to all ICUs.

Dr. Brochard disclosed that his research laboratory had received grants from several ventilator companies, but he had no disclosures related to the use of sedation in intensive care. ■

High Supine BP Signaled Lower 1-Year Mortality

BY MARY ANN MOON
Elsevier Global Medical News

In patients admitted to an intensive care unit for chest pain, higher supine systolic blood pressure correlates with lower mortality 1 year later, according to a report in the March 24/31 issue of JAMA.

The finding, from a Swedish study of more than 119,000 patients, confirms similar results from other research—including a prospective U.S. study involving more than 17,000 patients with acute chest pain, in which a systolic blood pressure less than 200 mm Hg at admission was associated with a poor prognosis at 6 months.

"Our study results support the feasibility of incorporating systolic admission BP in risk scoring models," reported Ulf Stenestrand, M.D., Ph.D., and associates at Linköping (Sweden) University (JAMA 2010;303:1167-72).

High systolic blood pressure with acute chest pain, in the stressful setting of an ICU, should not be confused with high ambulatory blood pressure. The study results apply only to the initial blood pressure taken in the high-stress context, the investigators noted.

Dr. Stenestrand and his colleagues examined the relationship between initial systolic blood pressure and long-term mortality using data within a registry of all patients admitted to medical ICUs in all Swedish hospitals between 1997 and 2007. The large sample size (119,151 patients) made it possible to assess the link in several subgroups, such as patients with diabetes and those whose chest pain was because of myocardial infarction. The mean follow-up was 2.5 years.

Patients in the highest quartile of supine systolic blood pressure at ICU admission had the lowest 1-year mortality, while those in the lowest quartile of blood pressure had the highest 1-year mortality. Patients showed progressively better mortality rates with increasing levels of blood pressure at ICU admission.

Compared with the reference group of patients in the second quartile (those with a blood pressure of 128-144 mm Hg at ICU admission), patients in the fourth quartile (blood pressure at least 163 mm Hg) had a 22% lower risk of death at 1 year, while those in the first quartile (blood pressure less than 128 mm Hg) had a 40% greater risk of death at 1 year.

That pattern showed no change when the data were adjusted for body mass index or conditions such as diabetes, dementia, malignancy, and a previous MI or stroke. It also remained constant when the follow-up time was extended to 3 years. In addition, the relationship was constant within all the subgroups of patients studied, including the nearly 44,000 who had a discharge diagnosis of MI.

The authors did not report any financial conflict of interest. ■

Pulmonary Perspectives

Chest Imaging and Radiation Exposure Reduction

Media coverage of excessive radiation doses from CT scans has led to increased public awareness of the health risks of ionizing radiation from CT scans. The number of CT scans performed annually in the United States increased from 3 million in 1980 to more than 70 million in 2007 (Amis et al. *J Am Coll Radiol* 2007;4[5]:272). The National Cancer Institute projects 29,000 excess cancers, with an estimated 50% case fatality rate, from the 72 million CT scans that Americans received in 2007 alone (Berrington de González et al. *Arch Intern Med* 2009;169[22]:2071).

While there is some disagreement over the extent of the cancer risk associated with exposure to radiation from medical imaging, there is broad agreement that steps can and should be taken to reduce unnecessary radiation exposure.

On February 9, 2010**,** the US Food and Drug Administration (FDA) announced an initiative to reduce unnecessary radiation exposure from three types of medical imaging procedures: computed tomography (CT), nuclear medicine studies, and fluoroscopy. The FDA is advocating the adoption of the following two principles of radiation protection:

1. Appropriate justification of the radiation procedure.

2. Optimization of the radiation dose used during each procedure.

Dr. Jeffrey Shuren, JD, director of the FDA Center for Devices and Radiological Health, elaborated by saying, "The goal of FDA's initiative is to support the benefits associated with medical imaging while minimizing the risks …*to help patients get the right imaging exam, at the right time, with the right radiation dose*" (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm200085.htm). In support of this goal, the FDA is launching a cooperative, "Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging."

Radiation Doses

Background radiation is estimated at 3 millisievert (mSv) per year at sea level. Of this, 2 mSv is estimated to come from radon exposure in American homes. Annual background exposure may range up to 4.5 mSv at high altitude. A transatlantic airplane flight increases radiation exposure by 0.03 mSv.

Radiation dose is often equated to a number of chest radiographs for comparison. A single chest radiograph is equivalent to 10 days of background radiation. A single conventional chest CT scan may provide 7 to 10 mSv of radiation exposure. Dose reduction strategies can reduce this exposure by at least two-thirds. The radiation exposure from a PET-CT scan is approximately 25 mSv. This higher level is more difficult to reduce further since the CT scan for attenuation correction is performed with a low radiation dose.

Incorporation of greater awareness of radiation dose in the selection of medical imaging is particularly important when imaging chest disease. These radiation doses are important as radiosensitive breast tissue is unavoidably included in chest CT scan examinations. Radiation-induced lung cancer and lymphoma are also of specific concern as a result of chest CT scans.

One chest CT scan leads to another, whether to verify the benign nature of an indeterminate pulmonary nodule or to assess treatment for cancer, suggesting more careful consideration of scan timing, as well as type of scan and CT scan dose. As a result, the three-pronged FDA Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging will (1) promote the safe use of medical imaging devices; (2) support informed clinical decision-making; and (3) increase patients' awareness of their own exposure.

The FDA intends to issue targeted requirements for manufacturers to incorporate important safeguards into the design of their machines to develop safer technologies and provide appropriate training to support safe use by practitioners. Input for establishing these requirements is being addressed with a public meeting, March 30-31, 2010.

Examples could include the following: a requirement that these devices display, record, and report equipment settings and radiation dose; an alert for users when the dose exceeds a diagnostic reference level (the optimal dose for most patients); training for users; and a requirement that devices be able to capture and transmit radiation dose information to a patient's electronic medical record and to national dose registries.

In addition, the FDA and the Centers for Medicare & Medicaid Services are collaborating to incorporate key quality assurance practices into the mandatory accreditation and conditions of participation survey processes for imaging facilities and hospitals. These quality assurance practices will improve the quality of oversight and promote the safe use of advanced imaging technologies in those facilities.

The FDA recommends that health-care professional organizations continue to develop, in collaboration with the agency, diagnostic radiation reference levels for medical imaging procedures and increase efforts to develop one or more national registries for radiation doses. A dose registry would pool data from many imaging facilities nationwide, capturing dose information from a variety of imaging studies. This registry will help define diagnostic reference levels where they do not yet exist, validate levels that do exist, and provide benchmarks for health-care facilities to use in individual imaging studies.

To empower patients and increase awareness, the FDA is collaborating with other organizations to develop and disseminate a patient medical imaging history card. This tool, which will be available on the FDA Web site, will allow patients to track their medical imaging history and share it with their physicians, especially when it may not be included in their medical records.

As a result of the recent publication of higher than expected CT scan dosages at noted institutions, CT scan volume has diminished in many institutions, with a coincident rise in requests for an MRI examination, often by patient request rather than by clinician. Unfortunately, these requests are not always appropriate for patient care. MRI is not a useful modality for following indeterminate pulmonary nodules. MRI is equivalent to CT scanning for evaluation of mediastinal lymphadenopathy and quite valuable for evaluation of disease spanning compartments, such as malignant pleural mesothelioma that may invade the chest wall, mediastinum, and abdomen.

MRI may be more useful for assessment of lungs in the future; but, at this time, the more common decision is between diagnostic chest CT scan and PET-CT scan. The information that is gained differs significantly, as does the radiation dose.

The chest CT scan provides superior anatomic information and the most precise detection and measurement for small pulmonary nodules. Chest CT scans include adrenal glands that are frequent sites of lung cancer metastasis. The brain is another important site of lung cancer metastases, although it is not adequately imaged by PET-CT scanning, even when brain images are obtained.

There are tumors that respond to chemotherapy by becoming biologically inactive without decreasing significantly in size. Evaluation of therapy for such a tumor may require PET-CT scanning. PET-CT dose differentiation is also less when disease in multiple organs would require CT scans of chest, abdomen, and pelvis. Minimizing the number of scans, including adoption of guidelines, such as the Fleischner Guidelines, for incidentally detected pulmonary nodules can decrease cumulative CT dose significantly (MacMahon et al. *Radiology* 2005;237[2]:395).

Chest CT dose can be reduced significantly without loss of diagnostic accuracy or adverse effect upon nodule measurement. Lungs offer maximal contrast between air and soft tissue, allowing marked reduction of radiation dose. Tube currents have been reduced up to 90% for lung cancer screening CT studies. The voltage also is now being reduced for CT pulmonary angiography.

While radiologists apply the principle of ALARA (as low as reasonably achievable), the radiation dose for a particular patient's chest CT scan can often be reduced by specifically requesting a low dose technique. This approach can be used in novel ways, such as for CT scans evaluating resolution or progression of a pneumothorax or pleural effusion.

Two additional considerations will reduce cumulative dose to a patient from chest CT scanning. Treat an acute process adequately before obtaining a CT scan for evaluation of nonacute findings. Pleural effusions and inflammatory opacities may limit visualization of small pulmonary nodules. An acute process that precludes adequate breath-hold may also result in a nondiagnostic CT scan that will ultimately require repetition.

As a general guideline, incidental nodule follow-up should be performed on an outpatient basis when the patient is well rather than while hospitalized for an acute process.

Acute and dynamically changing processes are often studied too frequently by CT scanning. Understanding, utilizing, and treating the information gleaned from one CT scan for an acute process may allow confident radiographic follow-up for up to a week or more. ■

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Division of Thoracic Imaging
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Dr. Marilyn G. Foreman, FCCP
Editor, *Pulmonary Perspectives*

Dr. Loren J. Harris, FCCP
Deputy Editor, *Pulmonary Perspectives*

Editor's Insight

As pulmonary and critical care physicians, thoracic imaging is crucial in our care of patients. The concern that radiation dose may widely vary among CT scanners is of particular concern, especially as patients may require serial examinations to assess stability or resolution of lesions.

This article is a logical progression from the report by Kerri Wachter in the November 2009 *CHEST Physician*. In the current article, Dr. Jacobson describes the new initiatives and possible solutions to the problem of excess radiation exposure in patients. As a thoracic radiologist, she offers practical advice for choice of procedures.

We look forward to the development of new guidelines for standardization of radiation dose in order to limit excess radiation exposure in our patients.

NETWORKS

Members in Industry, Dyspnea in End-of-Life Care

Palliative and End-of-Life Care

In March 2010, *CHEST* published a new ACCP Consensus Statement, American College of Chest Physicians Consensus Statement on the Management of Dyspnea in Patients With Advanced Lung or Heart Disease (*Chest* 2010;137[3] 674), sponsored by the ACCP Palliative and End-of-Life Care NetWork. The effort was chaired by Dr. Donald A. Mahler, FCCP, and written by an expert panel of specialists in pulmonary medicine, cardiology, nursing, and palliative care.

This project responded to the understanding that patients with advanced lung or heart disease were not consistently and effectively treated for relief of dyspnea. The statement summarizes available evidence regarding the care and treatment of dyspnea in those with advanced progressive illness. Based on results of a literature review from 1966 to 2008 and a rigorous consensus process, 20 statements cover five domains: measurement of patient-reported dyspnea, oxygen therapy, nonpharmacologic therapies, opioid medications, and ethical issues.

The statement endorses routine assessment of the intensity of a patient's dyspnea as part of a comprehensive care plan that includes inquiry into the distress, meaning, and unmet needs that accompany breathlessness. Healthcare professionals have an ethical obligation to treat dyspnea directly and communicate well with patients and families regarding palliative options for care that include cultural sensitivity.

Therapies cited include appropriate use of oral and/or parenteral opioids, consideration of noninvasive positive-pressure ventilation, and nonpharmacologic management. For patients who are hypoxemic at rest, supplemental oxygen is also cited as an evidence-based intervention that can provide relief of dyspnea.

This important statement extends the College's commitment to improve the cardiopulmonary health for those suffering from dyspnea beyond particular disease-oriented therapies.

Dr. Paul Selecky, FCCP; and
Dr. Richard Mularski, FCCP
Steering Committee Members

Thoracic Oncology

The Thoracic Oncology NetWork has been busy this last year addressing common issues in lung cancer care. The Thoracic Oncology NetWork is currently collaborating with the Society of Thoracic Surgeons on a project to develop a systematic review of data regarding management of the high-risk patient with early stage lung cancer.

The NetWork project, "ACCP Consensus Statement on the Classification of Autofluorescence Bronchoscopy Imaging and Pathologic Correlation for Preinvasive Squamous Cell Carcinoma of the Lung" is in the editing phase and near completion. The results of a survey of the Thoracic Oncology NetWork members, "Lung Cancer Beliefs," are currently being reviewed.

NetWork Highlights accepted for the program for CHEST 2010 are "From the Pathologist to the Patient: Practical Implications of the New Lung Adenocarcinoma Histologic Classification" and "Beyond 5-Year Mortality: Challenges Faced by the Long-term Lung Cancer Survivor." The CHEST 2010 NetWork Open Meeting is scheduled for Tuesday, November 2, 2010. Dr. Annette McWilliams, FCCP, will review the current data and trials for chemoprevention in lung cancer.

To find out more about the Thoracic Oncology NetWork, contact Jennifer Nemkovich at jnemkovich@chestnet.org.

Dr. John A. Howington, FCCP
NetWork Chair

Transplant

Lung transplantation is an important therapeutic option for patients with end-stage lung disease. However, this option remains limited by the shortage of donor lungs relative to transplant candidates.

In May 2005, the Organ Procurement and Transplant Network (OPTN) implemented the "Lung Allocation Score" system (LAS), which dramatically changed the strategy of lung allocation in the United States. Prior to the change, lung allocation was determined primarily by time accrued on the waiting list.

The LAS prioritizes candidates who are in most urgent need and who will most likely benefit from transplantation. Transplant benefit is determined by predictive models that weigh medical urgency against expected outcomes.

The goals of the LAS are to reduce wait-list mortality by prioritization of sicker patients and de-emphasize the role of waiting time (Egan et al. *Am J Transplant* 2006:6[5]:1212).

The LAS ranks candidates (ages 12 years and older) based on a scale from 0 to 100, which is determined by clinical data, including: disease, functional status, exercise capacity, lung and renal function, hemodynamics, and the need for oxygen or ventilator support. An update of these parameters is required at least every 6 months.

Questions regarding the LAS include whether it will achieve its goals without compromising posttransplant outcomes and whether patients with specific diseases are disadvantaged using the LAS. An interest in evaluation of the LAS in the context of longer-term outcomes also exists.

Ongoing refinements of the LAS are mandated by the OPTN with reviews of the system every 6 months. As more transplants occur under the new system, key outcomes will be more reliably assessed, leading to more robust conclusions regarding the pros and cons of the new allocation system.

Dr. Deborah Jo Levine, FCCP
Steering Committee Member

Members in Industry

The Members in Industry NetWork includes ACCP members who are employed in the pharmaceutical, biotechnology, and device industries, as well as nonindustry members interested in these areas. The NetWork encourages an exchange of views between ACCP members within and outside of industry. In order to facilitate this exchange, it is important to have a basic understanding of the roles health-care professionals play in industry.

Health-care professionals are involved in virtually all aspects of bringing new products to the bedside. The most common roles that practicing physicians will find their industry colleagues performing are clinical development and medical affairs.

Clinical Development divisions are generally responsible for exploring the safety and effectiveness of the candidate product upon completion of basic testing on normal volunteers. Once target disease areas for the product have been identified, Clinical Development conducts proof of concept trials through Phase III approval studies, as well as mandated postapproval studies or those needed to gain additional indications. While industry members have a wide array of skills and resources, they lack direct access to patients and highly honed treatment skills. These needs bring Clinical Development to the practicing clinician's door.

Medical Affairs divisions provide a wide array of services to practitioners and patients from late stage trials through end of product production. Members monitor safety issues, update critical documents, manage requests for support from external researchers, and administer information hotlines. Medical Affairs colleagues also handle requests for support of educational grants, including those providing CME; however, these individuals are often isolated from the external medical community to avoid actual or perceived influence. The companies may not influence selection of CME presenters.

There are several ways for practitioners to access Clinical Development and Medical Affairs personnel. Sometimes, company sales professionals can provide basic contact information, and usually it is available on company Web sites. Alternatively, directors of pharmacy and procurement services within hospitals often have this information due to their interactions with industry.

Pharmaceutical, biotechnology, and device companies have significant needs that only practicing clinicians can provide and possess significant resources that can benefit patients. Physicians and pharmacists in industry act as a bridge to bring these communities together for the benefit of all.

Dr. Mark Forshag, FCCP
NetWork Chair

The Year of the Lung Makes News

BY JENNIFER STAWARZ
Senior Manager, Public Relations

The American College of Chest Physicians (ACCP) and 2010: The Year of the Lung (YOL) have been featured in a cover story in the March issue of *Advance for Respiratory Care and Sleep Medicine*, a trade magazine that goes to over 45,000 pulmonary care professionals around the world.

There is a cover photo and interview with ACCP President Dr. Kalpalatha Guntupalli, FCCP, as well as an inside photo of Dr. Nicola Hanania, FCCP. The story captures the essence of the YOL campaign and gives details about ACCP and CHEST Foundation initiatives, as well as those sponsored by other Forum of International Respiratory Societies members.

The Advance magazine article highlighting 2010: The Year of the Lung can be accessed online at respiratory-care-sleep-medicine.advanceweb.com.

2010: The Year of the Lung is a global initiative instituted by the Forum of International Respiratory Societies, a collaboration of leading professional respiratory organizations. The 2010: The Year of the Lung campaign raises awareness of and advocates for lung health globally and locally. Visit www.chestnet.org/accp/year-lung.

The cover image and URL link have been reprinted with permission from ADVANCENewsmagazines.

FROM THE CEO

Here, There, Everywhere

BY PAUL A. MARKOWSKI, CAE

While my goal is to be in Northbrook on a regular basis, working with the great team that has been put together, I have had an enlightening few months of traveling to various venues to meet with our members, collaborative societies, and potential new partners.

I have witnessed the hard work done by many of our volunteer members and leaders, whose efforts on committees, such as, but not limited to, the CHEST Program Committee, ACCP-SEEK, and the Lung Cancer Guideline Committee, are amazing. I have been in the warm weather parts of this country when it has been unseasonably cold and in the cold weather parts when it has been unseasonably warm. One of these days, maybe I'll get the weather and my travel coordinated.

At the ACCP headquarters, we have been hard at work preparing for the spring Board of Regents meeting that will focus mainly on strategic planning. The results from our member survey, as well as a comprehensive look at our 2010 environmental snapshot, will be presented and discussed. This will assist us in taking a strategic direction that will best position the College to succeed in this rapidly changing environment.

All of this is really leading us forward to CHEST 2010 in Vancouver. I hope you were able to witness some of the 2010 Olympic and Paralympic Winter Games. You probably saw the wonderful climate, bright clear skies, and modern, upbeat, and cosmopolitan city. You can expect that and more—great restaurants, biking, walking, music, and, most important, high-quality education.

Our members planning the education program for CHEST 2010 are working tirelessly with our staff to provide you with the most relevant, cutting-edge education available anywhere.

Since this is the first CHEST meeting since I officially became the ACCP EVP and CEO, I am doing my best to make sure our leaders, members, and staff have all the resources and support that I can muster, while staying out of their way.

By the time you read this column, we will be well on our way to charting an exciting and successful future for the ACCP.

Now, let's bring on that spring weather. ■

MR. MARKOWSKI *is Executive Vice President and Chief Executive Officer of the American College of Chest Physicians.*

This Month in *CHEST*: Editor's Picks

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

► **Clinical Findings and Demographic Factors Associated With ICU Admission in Utah Due to 2009 Novel Influenza A (H1N1) Infection.** *By Dr. R. R. Miller III, et al.*

G/W EDITORIAL

► **Should We "Rescue" Patients With 2009 Influenza A (H1N1) and Lung Injury From Conventional Mechanical Ventilation?** *By Dr. R. D. Hubmayr, FCCP; and Dr. J. C. Farmer, FCCP.*

► **Upper Esophageal Sphincter and Gastroesophageal Junction Pressure Changes Act To Prevent Gastroesophageal and Esophagopharyngeal Reflux During Apneic Episodes in Patients With Obstructive Sleep Apnea.** *By Dr. S. Kuribayashi, et al.*

► **The Natural Viral Load Profile of Patients With Pandemic 2009 Influenza A (H1N1)) and the Effect of Oseltamivir Treatment.** *By Dr. I. W. Li, et al.*

TOPICS IN PRACTICE MANAGEMENT

► **Diagnosis of Adult Hereditary Pulmonary Disease and the Role of Genetic Testing.** *By Dr. P. Shah, et al.*

RECENT ADVANCES IN CHEST MEDICINE

► **Clinical Management of Pandemic 2009 Influenza A (H1N1) Infection.** *By Dr. D. S. Hui, FCCP, et al.*

Critical Care Commentary

Pathophysiology and Diagnosis of Heparin-Induced Thrombocytopenia

Heparin is one of the most widely used parenteral drugs in modern medicine, with approximately 12 million patient exposures annually in the United States alone. Although generally safe and effective, heparin use is associated with several side effects, the most potentially serious of which is heparin-induced thrombocytopenia (HIT). This condition affects between 0.1% and 3% of patients exposed to heparin products.

The variable frequency is due to several factors, including the type of heparin used (low-molecular-weight heparin [LMWH] is less immunogenic than unfractionated forms), route of administration (IV heparin is more likely to cause HIT than that given subcutaneously), and the type of laboratory test used to confirm the diagnosis.

Dr. Neil Halpern, FCCP
Section Editor,
Critical Care Commentary

HIT is an immune-mediated reaction caused by an antibody to the complex formed between heparin (H) and platelet factor 4 (PF4) that is released from activated platelets (Kelton et al. *Blood*. 1994;83[11]: 3232). IgG forms of the H-PF4 antibody bind to platelets via their FcIIa receptors, resulting in intense platelet activation, release of highly procoagulant microparticles, and, ultimately, intravascular thrombin formation. Thrombin causes additional platelet activation and fibrin clot formation and a worsening cycle of serious hypercoagulability that demands early recognition and prompt and appropriate treatment.

Despite the apparent etiology of HIT, the condition is not a typical immune response. For example, the IgG antibody response is relatively rapid and may occur without IgG class precedence; the antibody persistence is limited, and repeat heparin exposure often does not restimulate antibody production (Selleng et al. *Transfusion*. 2009;49[9]:1812). H-PF4 antibodies may be generated in patients with lupus and antiphospholipid syndrome, and HIT-like syndromes with positive laboratory tests have been reported in patients with acute infectious diseases without heparin exposure. Indeed, there is evidence that H-PF4 antibodies are part of an innate bacterial defense system (Greinacher J. *Thromb Haemost*. 2009;7[suppl 1] 9).

The clinical diagnosis of HIT should be considered if the platelet count falls by 50% or greater, with or without venous or arterial thrombosis, in a patient currently or recently receiving heparin therapy. Such patients may have other reasons for thrombocytopenia or thrombosis and do not have HIT. Nevertheless, since HIT can present in several diverse ways, it is important to include it in the differential diagnosis.

HIT may present systemically or locally with skin lesions at the heparin injection site. Most HIT cases (~70%) present 4 to 10 days after heparin exposure (Warkentin TE. *Semin Hematol* 1998;35[4 suppl 5]:9), but a rapid onset (within 24 h) form of HIT (~30% of cases) may occur in patients with an existing circulating H-PF4 antibody (Warkentin and Kelton. *N Engl J Med*. 2001;344[17]:1286).

Because these antibodies are usually transient—90% have disappeared from circulation within 3 months—rapid-onset HIT is typically associated with recent heparin exposure. Indeed, circulating H-PF4 antibodies are found in 10% of patients presenting to the ED with chest pain or symptoms of thrombosis and a history of recent (within 6 months) hospitalization (Francis et al. *Am J Emerg Med*. 2007;25[3] :279). Such patients are at higher risk of developing rapid onset HIT. A minority of patients present 2 to 6 weeks after heparin therapy with delayed-onset HIT (Rice et al. *Ann Intern Med*. 2002;136[3]: 210) that 'can be particularly difficult to recognize, as a history of heparin exposure may be elusive.

The recognition of HIT largely depends on regular monitoring of the

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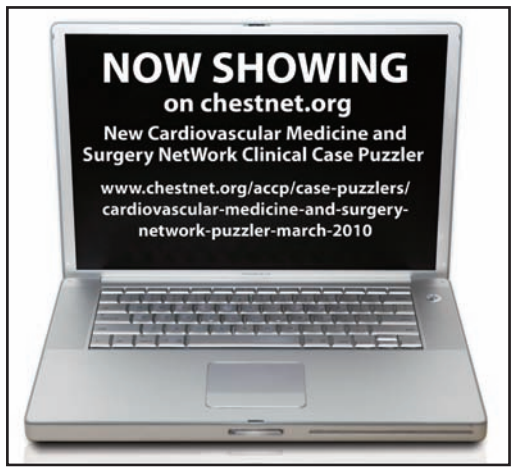
platelet count (Warkentin et al. *Chest*. 2008;133[suppl]:340S). Platelets should be measured at least every other day between days 4 and 14, in postoperative patients receiving therapeutic unfractionated heparin, while earlier monitoring is recommended for patients with a history of recent (within 3 months) heparin exposure, because of the risk of rapid onset HIT.

Postoperatively, patients receiving LMWH require monitoring every 2 to 3 days after day 4, while medical/obstetrical patients receiving LMWH do not require regular monitoring.

Using thrombocytopenia as a marker of HIT is problematic in the cardiac surgery setting, as significant platelet decreases occur in most patients. The platelet count typically begins to rise by the second or third day after cardiac surgery, but most patients do not develop the H-PF4 antibody until day 4 or 5. Thus, this early postoperative fall is not a sign of HIT without other supportive clinical signs.



In contrast, a secondary fall in the platelet count, or a failure of the platelet count to recover, may indicate HIT (Pouplard et al. *Br J Haematol*. 2005; 128[6]:837). Thrombocytopenia is also common in the ICU, although the incidence of HIT is less than 1%, despite positive H-PF4 antibody test results in 10 to 30% of medical, neurotrauma, or shock-trauma patients in the ICU (Levine et al. *J Thromb Thrombolysis*. [published online ahead of print, November 13, 2009]).

The laboratory diagnosis of HIT rests on the demonstration of a circulating H-PF4 antibody. The most widely available test is the enzyme-linked immunoassay (ELISA), although this assay carries a high rate of false-positive results, the scale of which depends on the clinical scenario. For example, 40 to 60% of postcardiac surgery patients develop a positive ELISA in the absence of clinical HIT (Francis et al. *Ann Thorac Surg*. 2003;75[1]:17).

Thus, the specificity of the ELISA for clinical HIT is relatively low in this setting, and, as discussed below, the physician must interpret the result in the light of the pretest clinical findings. On the other hand, its high sensitivity for H-PF4 antibodies means that a negative test result virtually excludes the diagnosis.

Recently, rapid immunoassays suitable for the near-patient setting have become available. One of these, the PIFA® heparin/PF4 immunoassay is approved for use in the United States, but, in the author's experience, correlates very poorly with the ELISA.

Many laboratories report ELISA test results simply as positive or negative. However, the diagnostic specificity is increased by knowing the actual optical density value, as high values (eg, >1.5) are more likely to be associated with a platelet-activating antibody and, thus, clinical HIT. Most commercially available ELISAs detect H-PF4 antibodies of IgG, IgA, and IgM specificities. However, since platelet activation in HIT is dependent on their FcIIa (IgG) receptors, detection 'of only IgG antibodies provides better diagnostic information without loss of sensitivity (Bakchoul et al. *J Thromb Haemost*. 2009;7[8]:1260).

The highest specificity for HIT is yielded by the serotonin release assay, which is based on the ability of H-PF4 antibodies to activate normal donor platelets in the presence of therapeutic amounts of heparin. Although the serotonin release assay is the "gold standard" of HIT tests, it is a complicated assay that is available in only a few centers.

Because of their low specificity, the ELISA results must be interpreted in light of the pretest probability of HIT.

The "4-T" score is a clinically validated assessment tool that takes into account the presence and timing of thrombocytopenia and thrombosis and whether other causes of these are present (Warkentin. *Br J Haematol*. 2003; 121[4]:535). Testing should only be performed when there is clinical evidence of HIT, since there is a danger of overdiagnosis if a positive ELISA is considered confirmatory in the absence of supportive clinical findings (Lo et al. *Am J Hematol*. 2007;82[12]:1037).

In patient populations where thrombocytopenia and heparin use are common, for example, in the ICU, the 4-T score, preferably coupled with knowledge of the ELISA optical density, an IgG-specific immunoassay, or serotonin release assay test, will be helpful in the differential diagnosis.

Because of its higher specificity, a strongly positive serotonin release assay is far more likely to indicate HIT than a weakly positive ELISA result, although a negative ELISA result has a high negative predictive value.

Repeating the ELISA in patients with low pretest probabilities of HIT is also problematic, as a significant number with an initially negative test result subsequently retest as positive (Chan et al. *Am J Hematol*. 2008;83[3]:212). Although repeat laboratory testing is justified if the pretest probability increases, there is a danger of overdiagnosis in scenarios where a positive ELISA is common without clinical symptoms of HIT (ie, open heart surgery).

In our experience, requests for HIT testing often coincide with the platelet nadir that occurs 2 to 3 days after heart surgery, yet most (>90%) of these test results are negative. However, if the test is repeated 2 to 3 days later, many patients will test positive, even if the platelet count is recovering, because of the natural history of H-PF4 antibody formation in this setting.

There is a similar risk of overdiagnosis in patients in the noncardiac surgical ICU, where the frequency of positive ELISA test results may increase almost threefold within 7 days of admission (Levine et al., *Thrombosis and Haemostasis*, in press).

In summary, HIT is a clinicopathologic syndrome resulting from the formation of antibodies against a neoantigen formed when heparin binds to PF4. This results in one of the most hypercoagulable states known to clinical medicine. Early recognition and prompt treatment are the cornerstones of effective management. The most widely available laboratory tests for HIT lack specificity and should always be inter-preted with the clinical picture in mind. ■

Dr. John L. Francis
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Professor of Medical Education
University of Central Florida College of Medicine
Orlando, FL

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ACCP Members Descend on Washington, DC

17th Annual ACCP Capitol Hill Caucus Held at a Momentous Time

As federal lawmakers were negotiating historic health-care reform legislation and avoiding a 21% cut in Medicare physician payments scheduled to begin April 1, more than 80 ACCP members descended on Washington on March 8-9, 2010, for the 17th Annual ACCP Capitol Hill Caucus. Attendees met with representatives from 192 congressional offices to urge legislators to address the growing critical care workforce shortage, permanently repeal the flawed Medicare sustainable growth rate formula, and support a congressional resolution regarding 2010: The Year of the Lung.

On the first of this 1½-day event, participants assembled at The Fairfax at Embassy Row to receive background information about the priority legislative issues for chest medicine. Guest speakers included Dr. Atul Grover, FCCP, Chief Advocacy Officer, Association of American Medical Colleges; Richard Deem, Senior Vice President, American Medical Association; and Ellen Riker, Senior Policy Advisor, Holland & Knight.

Attendees also received insider tips and techniques to help influence elected officials from the "Advocacy Guru," Stephanie Vance. The dinner speaker was Dr. David Hunt, Chief Medical Officer, Office of the National Coordinator for Health Information Technology.

The following morning, participants reconvened in the historic Kennedy Caucus Room, formerly the Russell Caucus Room, on Capitol Hill to discuss health system reform with Senator Benjamin Cardin (D-MD), Representative Jan Schakowsky (D-IL-9), Senator Lindsey Graham (R-SC), and former Representative Jim Davis (D-FL-11).

Dr. Daniel A. Nader, FCCP, ACCP Governor for Oklahoma and a 2010 caucus attendee, noted that "The ACCP Capitol Hill Caucus is a tremendous experience and education in real-life politics."

Learn more about the legislative priorities for pulmonary, critical care, and sleep medicine, including, but not limited to, the ACCP Principles for Health System Reform and a free ACCP advocacy education podcast on the critical care workforce shortage at www.chestnet.org/accp/. There is *AMA PRA Category 1 Credit*™ available for this podcast.

You can help the ACCP amplify its message on Capitol Hill by using the ACCP Legislative Action Center at www.capwiz.com/chestnet/home to e-mail your own senators and representative. Urge them to address the current legislative priorities for pulmonary, critical care, and sleep medicine. ■

ELSEVIER GLOBAL MEDICAL NEWS

Attendees at the 17th Annual ACCP Capitol Hill Caucus met with representatives from 192 congressional offices to urge action on key legislative reforms.

PCCU Lessons

March

► **Acute Exacerbations of Idiopathic Pulmonary Fibrosis**
By Dr. Steven A. Sahn, FCCP

► **Stimulation Disorders of the Diaphragm**
By Dr. Mark E. Ginsburg

PCCU
PULMONARY AND CRITICAL CARE UPDATE

April

► **Renal Replacement Therapy in the ICU**
By Dr. John A. Kellum, FCCP; and Dr. Thomas Rimmele

► **Drug-Induced Lung Disease**
By Dr. Kevin M. Chan, FCCP; and Dr. Kristy A. Bauman

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Mesothelioma Guidelines Debut

Mesothelioma • *from page 1*

tools, said Dr. Krug, a thoracic oncologist at Memorial Sloan-Kettering Cancer Center in New York.

Two studies have reported that serum levels of osteopontin (N. Engl. J. Med. 2005;353:1564-73) and soluble mesothelin-related protein (Clin. Cancer Res. 2007;13:5076-81) are elevated in patients with pleural mesothelioma, suggesting that these markers may be useful as a screening test or may have prognostic significance.

The guidelines include principles of surgical resection for mesothelioma, although the role of aggressive surgery is controversial, Dr. Krug said.

Extrapleural pneumonectomy (defined as en bloc resection of the pleura, lung, ipsilateral diaphragm, and often pericardium) is associated with major complications in up to 40% of patients, as well as a 6% mortality rate, even in the hands of skilled surgeons.

Extrapleural pneumonectomy is considered the "best option" in the guidelines for early disease with favorable epithelioid histology in good-risk patients. Pleurectomy (or complete removal of the pleura and all gross tumor) may be a "better choice" for advanced disease, mixed histology, and/or high-risk patients.

As in the new NCCN non–small cell lung cancer guidelines, the recommendation is that resection should be performed by a board-certified thoracic surgeon.

After surgery, all patients should be referred for adjuvant therapy, which may include chemotherapy and radiation.

DR. KRUG

The guidelines note that after surgery, all patients should be referred for adjuvant therapy, which may include chemotherapy and radiation depending on tumor pathology and whether any preoperative therapy was used. Historically, mesothelioma is believed to be chemoresistant, especially the sarcomatoid variant, Dr. Krug said. Prognosis is generally poor.

A retrospective analysis of 663 patients with mesothelioma reported a median survival of 16 months with pleurectomy vs. 12 months with extrapleural pneumonectomy (J. Thorac. Cardiovasc. Surg. 2008;135:620-6). When pneumonectomy was combined with neoadjuvant chemotherapy, however, survival ranged from 17 to 29 months in three prospective studies.

"Clearly, there's a subgroup of patients who have a more prolonged survival with this aggressive approach," he said.

Pemetrexed (Alimta) and cisplatin administered every 3 weeks is the only first-line combination chemotherapy in the guidelines with an NCCN category 1 designation. A phase III study reported a median survival of 12.1 months with the combination vs. 9.3 months with cisplatin alone (J. Clin. Oncol. 2003;21:2636-44).

Other possible first-line regimens include pemetrexed plus carboplatin, gemcitabine (Gemzar) plus cisplatin, or monotherapy with pemetrexed or vinorelbine (Navelbine).

Only pemetrexed/cisplatin is approved by the Food and Drug Administration for first-line treatment, Dr. Krug said in an interview.

Data were extremely limited with regard to second-line chemotherapy, which can include pemetrexed (if it wasn't given as first-line therapy), vinorelbine, or gemcitabine.

The guidelines also set forth principles for radiation therapy, a task Dr. Krug described as "trying to shoot the peel off an apple without damaging the apple itself," referring to the difficulty in radiating the pleura with the lung intact and without causing pneumonitis. Adjuvant radiation therapy is recommended for patients after extrapleural pneumonectomy to improve local control, and is also an effective palliative treatment for relief of chest pain associated with mesothelioma.

Finally, the guidelines recommend that all patients be evaluated by a multidisciplinary team including radiation oncologists, surgeons, medical oncologists, diagnostic-imaging specialists, and pulmonologists for a multimodality treatment recommendation. ■

COLLEAGUE COMMENTARY

Dr. Richard Fischel, FCCP, comments: This is a very important topic. Despite the generally poor outcome seen in mesothelioma, it is impossible to begin appropriate therapy without accurately making the diagnosis first. Having NCCN guidelines to assist in making the diagnosis will provide those dealing with this disease the consistency needed to then evaluate the effectiveness of therapy. The brief review of therapeutic outcomes provided allows a glimpse into the current status of treatment and outcomes in this difficult disease.

Lung Cancer Strategies Target Resistance to EGFR Therapy

BY SUSAN LONDON
Elsevier Global Medical News

CORONADO, CALIF. — The advent of epidermal growth factor receptor inhibitors to treat EGFR-mutant lung cancer has been a "wonderful success," said Dr. Jeffrey Engelman of Massachusetts General Hospital Cancer Center in Boston. But the duration of response averages only about 10 months, and patients having these tumors tend to be younger.

"Telling a 40-year-old that you can give him a progression-free survival of 15 months, although exciting to us from a historical perspective, is obviously not really satisfactory to patients," he told an audience of lung cancer researchers and clinicians at a joint conference of the American Association for Cancer Research and the International Association for the Study of Lung Cancer.

"Clearly, these cancers are evolving, and they are able to become resistant to these therapies, and we somehow need to deal with the fact that these drugs (and others) are not working for longer," he said.

If Dr. Engelman's words cast a cloud, he also offered a glimpse of how resistance might be overcome. New molecular and physiologic insights are revealing ways of improving on lung cancer therapies that target EGFR, he reported.

EGFR inhibitors such as erlotinib (Tarceva) and gefitinib (Iressa) induce cell death by preventing downstream signaling in the PI3 kinase, MAP kinase, and other pathways, he explained. Over time, cancers can acquire resistance to these agents by two main mechanisms. They may develop a second mutation in the EGFR gene (e.g., the T790M mutation), or they can develop new ways of activating the downstream pathways. For example, amplification of the proto-oncogene MET or activation of the isulin-like growth factor–1 receptor (IGF-1R) can restore signaling.

Resistance due to the T790M mutation could be overcome with an irreversible EGFR inhibitor, according to Dr. Engelman. Two such agents have been disappointing with limited efficacy and dose-limiting toxicity in clinical trials, however. A new irreversible EGFR inhibitor in preclinical testing is showing a better profile.

Combined treatment with a MET inhibitor and an EGFR inhibitor could overcome resistance due to MET amplification, he continued. "This is a highly effective therapy in the right patient," he commented. "But the problem is that most patients who become resistant don't have this mechanism." Similarly, resistance due to IGF-1R activation could be overcome by combined treatment targeting both IGF-1R and EGFR.

Dr. Engelman disclosed that he has a patent regarding strategies to overcome resistance to EGFR inhibitors. ■

President Signs Landmark Health Reform Legislation

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

After more than a year of debate, President Barack Obama on March 23 signed comprehensive health reform legislation into law, clearing the way for approximately 32 million previously uninsured Americans to access health insurance in the next few years.

At a signing ceremony in the East Room of the White House, President Obama said it is time for the "overheated rhetoric" on reform to meet the reality of the changes.

The historic signing was made possible after a late-night vote in the U.S. House of Representatives on March 21 when lawmakers voted 219-212 to approve the health reform bill passed by the Senate last December. The bill (H.R. 3590) creates health insurance exchanges where individuals can shop for insurance that meets minimum coverage standards. It also requires individuals to obtain health coverage and bars insurers from discriminating against people based on gender or pre-existing medical conditions.

President Obama signed most of the health reform provisions into law on March 23. Later in the week, Congress passed a smaller bill—known as the reconciliation bill—that included corrections to the original package, including removal of some of the more controversial political deals from the law. The president signed that companion legislation later in March.

The reconciliation bill also included increased federal subsidies for Americans who can't afford to purchase health insurance and also lowered financial penalties for individuals who choose not to purchase insurance.

Of interest to physicians, the reconciliation bill increased Medicaid payments to primary care physicians. The bill requires that Medicaid payments be increased up to the level of Medicare payments for primary care physicians delivering primary care services in 2013 and 2014. It also increases funding for community health centers.

The bill also provides aid to Medicare beneficiaries who fall into the Medicare part D prescription drug "doughnut hole." This year, beneficiaries who enter the doughnut hole will get a $250 rebate. Next year, drug companies will be required to provide a 50% discount on brand-name drugs in the doughnut hole, rising to 75% on both brand-name and generic drugs by 2020.

The reconciliation bill also beefs up the insurance reform provisions of the Senate-passed bill. Under this new bill, the federal government would require health plans to provide coverage for nondependent children up to age 26 years within 6 months. It also bars group health plans from excluding people on the basis of pre-existing conditions starting in 2014. For children, plans would be barred from pre-existing conditions exclusions 6 months after enactment.

As passed by the House, the total legislative package would cover 32 million additional Americans, or about 94% of the population, according to the Congressional Budget Office. The CBO estimated the cost of the legislation at $940 billion over 10 years and said it would reduce the deficit by $143 billion from 2010 to 2019. ■

Health Reform Implementation Timeline

2010

Seniors whose prescription drug costs push them into the Medicare Part D doughnut hole receive a $250 rebate.

No new physician-owned hospitals may be built after Dec. 31.

Indoor tanning services are taxed at 10%, beginning as early as July.

Health plans are barred from excluding children due to pre-existing conditions, beginning as early as September.

Health plans are barred from dropping members due to illness.

Health plans that provide dependent coverage for children must cover them up to 26 years of age.

2011

A 10% Medicare bonus payment for primary care physicians begins and runs through the end of 2015.

A 10% Medicare bonus payment for general surgeons working in shortage areas begins and runs through the end of 2015.

HHS awards 5-year grants to states to develop alternative medical liability reform initiatives.

Medicare and Medicaid programs eliminate out-of-pocket costs for proven preventive services.

Unused specialty graduate medical education training slots can be used for primary care training.

Seniors whose prescription drug costs push them into the Medicare Part D doughnut hole receive a 50% discount on all brand-name drugs.

2012

Medicaid pilot tests bundled payments for episodes of care, including hospitalization.

Medicare provides incentives for physicians to form accountable care organizations.

Drug makers must report drug samples given to physicians if those drugs are covered by Medicare or Medicaid.

2013

Medicaid rates for primary care services are raised to at least Medicare rates, through 2014.

National pilot program tests bundled payment.

Health plans must adopt uniform standards for electronic submission of health information.

Drug and device makers must report any payments made to physicians and hospitals.

2014

Health insurance exchanges in each state open for individuals and small employers.

Health plans are barred from denying coverage based on pre-existing conditions.

Health plans are barred from charging higher fees based on health status or gender.

Health plans are barred from imposing annual limits on coverage.

Most individuals are required to obtain health insurance coverage or pay a fine.

Medicaid eligibility expands to individuals at 133% of poverty.

Independent Payment Advisory Board created.

ELSEVIER GLOBAL MEDICAL NEWS

How Health Reform and ACCP Principles Compare

BY DR. IRWIN BERLIN, FCCP
Chair, ACCP Government Relations Committee

The following is an overview of how The Patient Protection and Affordable Care Act compares with the ACCP Principles for Health System Reform established in the fall of 2009 and based on input from the ACCP general membership.

► **ACCP Principle 1: Provide all Americans with access to affordable and portable health insurance that does not exclude or discriminate against those with pre-existing conditions.**

The legislation would provide 32 million more Americans with health care coverage and removes many of the objectionable practices of the health insurance industry, such as discriminating against those with pre-existing conditions. Health insurers could not impose lifetime limits on the total amount of services covered, could rescind coverage only for certain reasons, would have to cover certain preventive services with no cost sharing, and would have to allow unmarried dependents to be covered under their parents' policies up to age 26 years.

► **ACCP Principle 2: Increase the effectiveness of critical care physicians by providing incentives for telemedicine use in both rural and underserved inpatient critical care settings.**

The legislation expects the Centers for Medicare & Medicaid Services (CMS) Innovation Center to test projects in inpatient settings (including ICUs) that facilitate the treatment of Medicare beneficiaries in their local hospitals through consultation and coordination with specialists at integrated health systems. These care coordination models would allow rural Medicare beneficiaries to receive acute inpatient services, including intensive care, at their local hospital with consultation from integrated health systems.

The criteria for care coordination models to be tested by the CMS Innovation Center would be expanded to facilitate inpatient care, including intensive care, of hospitalized Medicare beneficiaries at their local hospital. This would be done through the use of electronic monitoring by specialists, including intensivists and critical care specialists, based at integrated health systems.

► **ACCP Principle 3: Fund innovative, patient-centered approaches to critical care that support end-of-life counseling for critically ill patients and their families.**

The legislation does not address this issue specifically. The ACCP will continue to advocate for this issue going forward.

► **ACCP Principle 4: End the annual cycle of Medicare physician payment cuts.**

Continued on page 19

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Continued from page 17

The legislation does not address the flawed Medicare sustainable growth rate (SGR) formula, a critical component of health system reform. Action to permanently repeal the SGR formula was separated from health system reform legislation months ago.

The ACCP, working with organized medicine, is committed to bringing SGR legislation for a vote this spring in a separate piece of legislation.

► **ACCP Principle 5: Implement strong and effective medical liability reforms to reduce the costs of defensive medicine and medical liability insurance.**

The legislation establishes a competitive grant program for states to develop, implement, and evaluate innovative medical malpractice reforms. This is in addition to the $25 million medical liability reform alternative grant program that the administration initiated in September 2009, which is being implemented by the Agency for Healthcare Research and Quality (AHRQ).

While the legislation recognizes that medical liability contributes significantly to the costs of care, proven reforms were not included.

► **ACCP Principle 6: Health system reform should include national standardization of insurance credentialing, quality reporting, patient eligibility verification, claims submissions, and other reforms that will simplify and reduce administrative costs.**

The legislation would implement administrative simplifications, in addition to reporting requirements and incentive payments related to the physician quality reporting initiative (PQRI), including electronic prescribing and electronic health records.

The health system reform legislation signed by President Obama is an important step but far from the final step in health system reform.

THE ACCP WILL WORK TO PASS ADDITIONAL LEGISLATION TO CORRECT DEFICIENCIES AND ADOPT OTHER CRITICAL HEALTH SYSTEM REFORMS.

The ACCP will work vigorously to pass additional legislation to correct deficiencies and adopt other critical health system reforms. Bills will be introduced in the future to make important policy changes that were not incorporated in the reconciliation package.

The House and Senate will take up SGR reform legislation in the next couple of months.

Health system reform is best viewed as a journey, and there still is much work to do to realize many of chest medicine's priority objectives.

The ACCP will be relentless in pursuit of the unfinished business of health system reform and empowering our members and their patients to improve the health of our nation. ■

New FDA Panel Targets Menthol Cigarettes

BY ALICIA AULT
Elsevier Global Medical News

WASHINGTON — Flexing the Food and Drug Administration's new tobacco regulation powers, the first meeting of the agency's tobacco advisory panel focused scientific scrutiny on menthol cigarettes—with an eye to determining whether the menthol additive should be restricted or banned.

The FDA's new Tobacco Products Scientific Advisory Committee called on the tobacco industry to provide the FDA with a wealth of characterization, clinical effect, and marketing data about menthol cigarettes.

"I just want to get a sense of what the menthol cigarette product is about," said Dr. Neal L. Benowitz, chief of the division of clinical pharmacology at the University of California, San Francisco, and a member of the new tobacco advisory committee.

During the 2-day meeting at the end of March, Dr. Benowitz and his colleagues said they were interested in knowing how the industry manufactured menthol, how it was added to cigarettes, why it was added, and how manufacturers decide when to increase or decrease menthol levels. They also want to know what the substance does in the body—including chemosensory, neurologic, and behavioral effects—and how and why menthol was marketed to certain population groups.

"We want to know if targeted marketing strategies exist and their nature," said panel chairman Dr. Jonathan M. Samet, FCCP(Hon) of the University of Southern California, Los Angeles.

A number of health organizations have asked for a quick FDA assessment of menthol and a subsequent ban, including the American Medical Association, the American Public Health Association, the American Heart Association, and the Legacy Foundation.

The Tobacco Products Scientific Advisory Committee met for the first time since the FDA was given the power in June 2009 to regulate tobacco through the Family Smoking Prevention and Tobacco Control Act. The advisory panel is expected to provide the FDA with science-based recommendations for how best to establish and carry out its regulatory mission, said FDA Commissioner Margaret Hamburg at the meeting's opening.

"The FDA regulation of tobacco products is a science-based, science-driven process—it must be," Dr. Hamburg told the panelists. She also reminded them that their actions were likely to have consequences beyond U.S. borders. "You are setting standards and delineating pathways that will be followed by many others around the world," she said.

As part of the Tobacco Control Act, the FDA's tobacco advisory committee was required to submit a report and recommendations on menthol by March 2011.

The advisers heard conflicting data on menthol's properties and its potential harms. The federal government's National Survey on Drug Use and Health indicates that there are 19.2 million menthol smokers, about 1 million of whom are 12-17 years old, said Ralph S. Caraballo, Ph.D., epidemiology branch chief at the Centers for Disease Control and Prevention's Office on Smoking and Health.

The same survey data indicate that menthol cigarettes are preferred by women, by blacks, and by smokers who are younger than 18 years, said Dr. Caraballo.

THE PANEL WANTS TO KNOW HOW MENTHOL WAS MADE, WHY IT WAS ADDED TO CIGARETTES, AND THE REASONS IT WAS MARKETED TO CERTAIN GROUPS.

Studies showed that menthol smokers had higher levels of nicotine dependence and a more difficult time quitting, said Allison C. Hoffman, Ph.D., a scientist from the National Institute on Drug Abuse who is working temporarily for the FDA's new Center for Tobacco Products.

A review of the literature on marketing of menthol cigarettes found that the products were promoted as being healthier than nonmenthol cigarettes, added Dr. Joshua Rising, another official with the Center for Tobacco Products. Studies conducted by manufacturers found that adults perceived menthol cigarettes to be less harsh, said Dr. Rising. He also said that manufacturers' documents indicated that they had increased or decreased menthol levels in certain brands to attempt to build loyalty, especially among African Americans.

At least one cigarette maker, Lorillard Inc., maker of the menthol brand Newport, disputed the notion that menthol levels had been manipulated, saying that the company had provided data showing that Newport levels have not changed.

"Menthol does not make cigarettes more harmful, and the science supporting this conclusion is clear and compelling," said Dr. William True, senior vice president of the Lorillard Tobacco Company. He also denied that menthol appealed to young smokers in particular.

The Tobacco Products Scientific Advisory Committee would like more data from the industry by its next meeting, which is tentatively scheduled in July. ■

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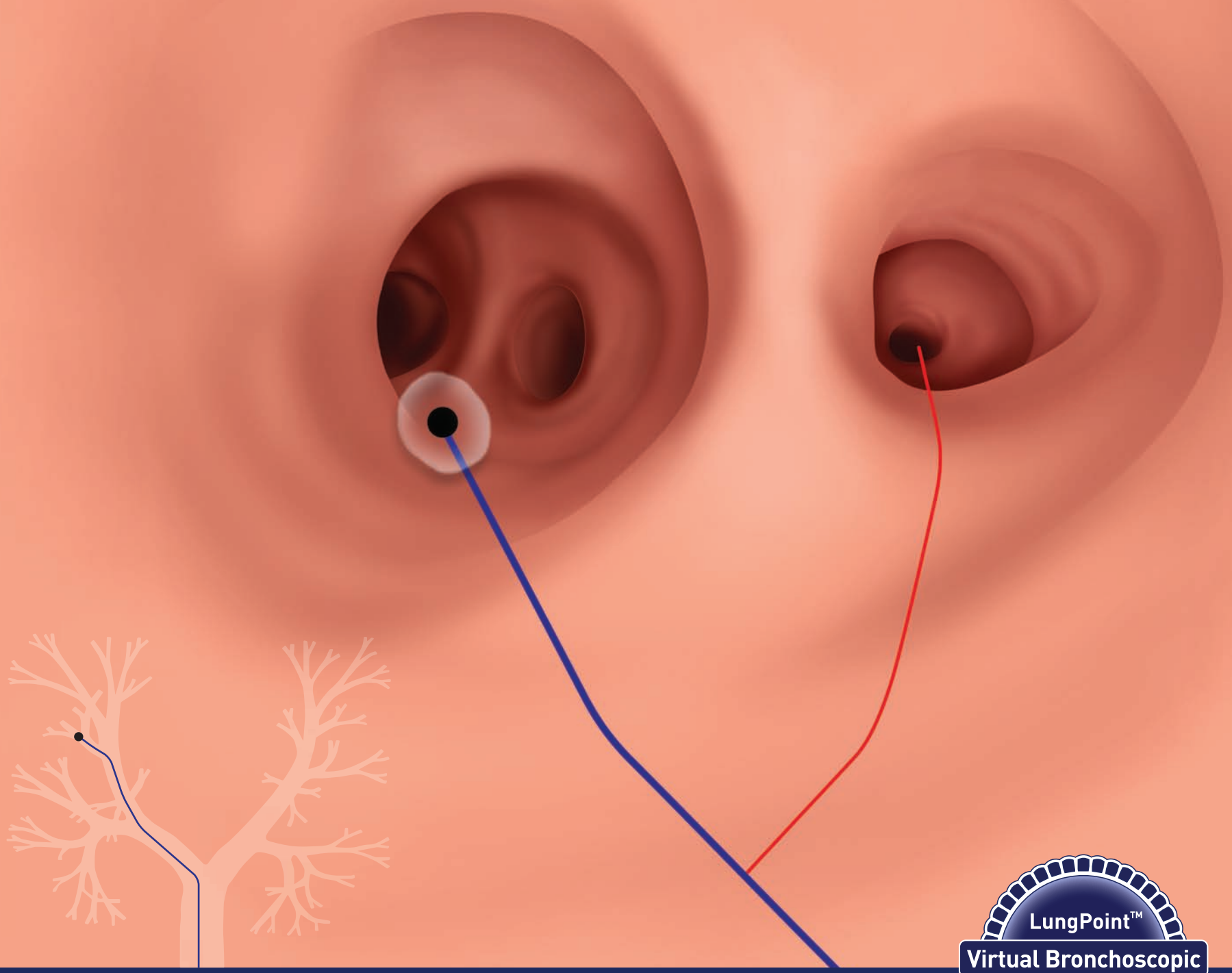

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