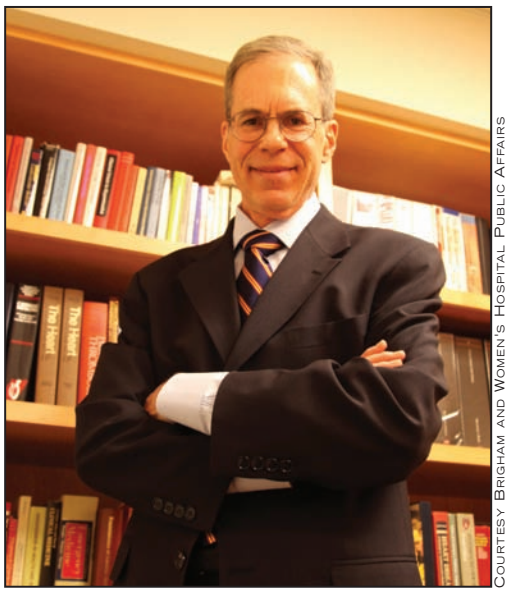
VOL. 7 • NO. 1 • JANUARY 2012

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

"I think ADOPT's gift to the medical community is to point the way toward a future trial … in which the comparison group allows VTE prophylaxis as it is really practiced – giving it in the hospital and not post discharge," Dr. Samuel Z. Goldhaber said.



COURTESY BRIGHAM AND WOMEN'S HOSPITAL PUBLIC AFFAIRS

ADOPT Nixes Extended Thromboprophylaxis

BY BRUCE JANCIN
Elsevier Global Medical News

ORLANDO – Prolonged thromboprophylaxis with 30 days of oral apixaban in initially hospitalized, acutely medically ill patients proved no more effective and caused more major bleeding than 6-14 days of enoxaparin in a major randomized clinical trial.

Results of the 6,528-patient Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial provided no support in the medically ill for the sort of multiweek extended prophylaxis against venous thromboembolism (VTE) that's routine in patients undergoing total hip replacement or other high-risk orthopedic surgery. But the ADOPT trial is very unlikely to be the final word on this issue, according to lead investigator Dr. Samuel Z. Goldhaber, FCCP, who presented the findings at the annual meeting of the American Heart Association.

Observers agreed with this assessment. They commented that the 13% relative risk reduction in VTE-related events seen in the apixaban group, while falling short of statistical significance, was actually encouraging in light of a few study design problems that stacked the deck against the investigational oral direct factor Xa inhibitor. They predicted that better-designed studies of extended thromboprophylaxis with apixaban or the other new oral anticoagulants are likely to come.

ADOPT was a double-blind, placebo-controlled trial conducted at 302 centers in 35 countries. It involved restricted-mobility patients hospitalized for medical conditions placing them at increased VTE risk, including heart failure, respiratory failure, cancer, acute rheumatic disorders, infection, and inflammatory bowel disease. Participants were randomized to oral apixaban at 2.5 mg twice daily for 30 days or subcutaneous enoxaparin at 40 mg once daily for 6-14 days followed by placebo.

See **ADOPT** • *page 2*

Pertussis Vaccine's Waning Immunity Cause of Epidemic

Efficacy 71% below optimum at 5 years.

BY MITCHEL L. ZOLER
Elsevier Global Medical News

BOSTON – The acellular pertussis vaccine's failure to deliver durable infection protection to children aged 7-10 years led to the 2010 California pertussis epidemic, and has prompted infectious diseases experts to question the current schedule of childhood pertussis vaccination.

"An increase in the risk of pertussis is occurring in the time since completion of the five-dose DTaP [diphtheria, tetanus, acellular pertussis] series, with similar trends seen in California, Minnesota, and Oregon," Sara Tartof, Ph.D., said at the annual meeting of the Infectious Diseases Society of America.

"Continued evaluation of DTaP duration of protection is needed to determine the appropriateness of timing of pertussis vaccinations," said Dr. Tartof, an epidemic intelligence officer in the Centers for Disease Control and Prevention's National Center for Immunization and Respiratory Diseases in Atlanta.

Dr. Tartof and a second CDC researcher presented results from two independent studies that both showed children faced a substantially increased rate of pertussis infection 4 or more years out from their fifth and final childhood vaccination, which these days usually occurs when U.S. children are 4 years old. Recent surges in U.S. pertussis cases, which began in 2005, and then spiked even higher in 2010, implicated the acellular vaccine as the cause.

"It certainly caused the 2010 California epidemic, and it happened in Minnesota and Oregon, too. Waning immunity with acellular pertussis led to

See **Vaccine** • *page 10*

INSIDE

Complaints Influence Final Rule on ACOs

BY ALICIA AULT
Elsevier Global Medical News

Use of electronic medical records is no longer a condition for participating in an accountable care organization, according to the final rule that will govern how ACOs are constructed and how they will be paid.

That change is just one of many in the long-awaited regulation. The 696-page final rule contains many significant changes that were made in response to the 1,320 comments the agency received on its proposed rule, published April 7 in the Federal Register.

Many physician groups and hospitals complained about various aspects of the proposed rule. They met repeatedly with the agency, then–CMS Administrator Donald Berwick said during a press briefing.

"Thanks to the generous input of ideas from so many Americans, we've been able to fine-tune and improve these rules to better meet the needs of a range of stakeholders," Dr. Berwick said.

See **ACOs** • *page 12*

CHEST Physician
60 Columbia Rd.,
Bldg. B, 2nd flr.
Morristown, NJ 07960

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

Risk Reduction Not Significant

ADOPT • *from page 1*

The primary efficacy end point was the 30-day composite of death related to VTE, fatal or nonfatal pulmonary embolism, symptomatic deep vein thrombosis, or asymptomatic proximal-leg deep vein thrombosis. This composite end point occurred in 2.71% of the apixaban group, compared with 3.06% in the enoxaparin arm, a 13% relative risk reduction.

The 30-day major bleeding rate was 0.47% in the apixaban group and 0.19% with enoxaparin. The resulting 2.58-fold increased relative risk of major bleeding in the apixaban group was significant.

A major study limitation was that one-third of the 6,528 participants couldn't be evaluated for the primary efficacy end point because they lacked a follow-up systematic bilateral compression ultrasound exam of the legs. As a result, the study was underpowered, and the 13% relative risk reduction didn't achieve statistical significance.

The purpose of the follow-up ultrasound was to detect asymptomatic proximal-leg DVT. The Food and Drug Administration required that this be part of the primary efficacy end point, even though compression ultrasonography after hospital discharge isn't routine practice and the clinical significance of asymptomatic VTEs remains unclear.

The other major problem with the ADOPT design was that the comparison arm didn't reflect real-world clinical practice, which is to stop enoxaparin prophylaxis at the time medically ill patients are discharged, as many find self-injection of enoxaparin too daunting. In ADOPT, the average length of stay was 5 days, but patients in the enoxaparin arm were on the low-molecular-weight heparin for 6-14 days, again as requested by the FDA.

Dr. Goldhaber, a cardiologist at Brigham and Women's Hospital in Boston, noted that as soon as enoxaparin prophylaxis stopped, the rate of VTE events in that study arm increased. A key secondary study end point – the rate of symptomatic VTE or VTE-related death after parenteral enoxaparin was stopped – occurred in 0.56% of the enoxaparin arm, compared with 0.25% in the apixaban arm, a 56% relative risk reduction favoring apixaban that just missed significance. This finding suggests that a strategy of extending thromboprophylaxis for longer than 6-14 days shows promise.

"I think ADOPT's gift to the medical community is to point the way toward a future trial that does not require ultrasound unless the patient is symptomatic and in which the comparison group allows VTE prophylaxis as it is really practiced – giving it in the hospital and not post discharge as in ADOPT," he said.

Dr. Elliott Antman, professor of medicine at Harvard Medical School, Boston, commented: "This is an important medical problem that needs to be adequately treated, and I don't think we're doing a good enough job now. I think if future trials restrict the end point to symptomatic venous thrombosis and the duration of treatment in the comparator arm is kept to the way we do it now, then we may see some real benefit for a drug like apixaban. Apixaban is, in my mind, still a very attractive agent for the prevention of venous thrombosis. We just need to learn how to design a trial to demonstrate what I think is the true benefit of these new oral anticoagulants."

He added, "There's a lot of discussion in the clinical research community about the importance of these ultrasound-detected venous thromboses, whether they truly translate into something that may impact on a patient or they perhaps just go away on their own. Including them in a primary end point, as in the ADOPT study, is really questionable in my mind."

Dr. Mary Cushman said that going forward it will be critical to develop validated risk prediction models to identify the medical inpatients at highest risk for postdischarge VTE. That's the right population to study in clinical trials.

The increased VTE risk in medically ill patients is known to extend for 3 months post discharge. An important question to address in future trials of the new oral factor Xa inhibitors is whether they should be utilized for that full 3-month risk period, rather than 1 month as in ADOPT, observed Dr. Cushman, professor of medicine and pathology at the University of Vermont, Burlington.

Dr. Goldhaber said he and his coinvestigators are now analyzing their nearly 7,000-patient database to identify key predictors of VTE for incorporation into a new risk prediction model.

Apixaban in ADOPT failed to hit the home run it did earlier for stroke prevention in the setting of atrial fibrillation in the ARISTOTLE trial conducted in more than 18,000 patients (N. Engl. J. Med. 2011;365:981-92).

Simultaneous with Dr. Goldhaber's presentation at the meeting, ADOPT was published online in the New England Journal of Medicine (doi:10.1056/NEJMoa1110899).

Dr. Goldhaber has served as a consultant to numerous pharmaceutical companies, including Bristol-Myers Squibb and Pfizer, which sponsored the ADOPT trial. Dr. Antman and Dr. Cushman declared no relevant financial interests. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Oral factor Xa inhibitors such as apixaban represent a major advance in the prevention of thromboembolic disease. It is currently approved in Europe for prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery. Although smaller studies have proved its effectiveness over enoxaparin, the ADOPT trial showed otherwise. In the real-world setting, we must be cautious as patients undergoing knee replacements may be older, have a higher burden of chronic disease, and have a higher risk of GI bleeding.

IN THIS ISSUE

CHEST PHYSICIAN Is Online
CHEST PHYSICIAN is available on the Web at www.chestnet.org/accp/chest-physician.

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

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, an Elsevier company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

The statements and opinions expressed in **CHEST PHYSICIAN** do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Elsevier Inc. do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

Address Changes: Fax changes of address (with old mailing label) to 973-290-8245.

POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

IMNG MEDICAL MEDIA

IMNG SOCIETY PARTNERS, A DIVISION OF IMNG MEDICAL MEDIA
President, IMNG Medical Media Alan J. Imhoff
Director, IMNG Society Partners Mark Branca
Editor in Chief Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck
Managing Editor Leanne Sullivan

Audience Development Manager Barbara Cavallaro, 973-290-8253, b.cavallaro@elsevier.com
Executive Director, Operations Jim Chicca
Director, Production and Manufacturing Yvonne Evans Struss
Production Manager Judi Sheffer
Creative Director Louise A. Koenig
Display Advertising Manager The Walchli Tauber Group: 443-512-8899, fax 443-512-8909, greg.pessagno@wt-group.com

ADVERTISING OFFICES 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250
CLASSIFIED ADVERTISING OFFICES The Walchli Tauber Group, 2225 Old Emmorton Rd., Suite 201, Bel Air, MD 21015, 443-512-8899
EDITORIAL OFFICES 5635 Fishers Lane, Suite 6000, Rockville, MD 20852, 240-221-4500, fax 240-221-2541

Early Thrombolysis Improves Long-Term DVT Outcomes

BY PATRICE WENDLING
Elsevier Global Medical News

SAN DIEGO – Catheter-directed thrombolysis added to standard therapy for deep vein thrombosis reduced the risk of post-thrombotic syndrome by 14.5%, but at an increased cost of bleeding among 209 patients in a randomized, controlled trial.

At 2 years, 55.6% of patients receiving standard anticoagulation and compression stockings developed post-thrombotic syndrome (PTS), compared with 41.1% receiving catheter-directed thrombolysis (CDT) plus standard therapy ($P = .047$) in the multicenter CaVenT study.

The number needed to treat to prevent one PTS was seven, Dr. Per Morten Sandset and his colleagues reported in a late-breaking abstract presented at the annual meeting of the American Society of Hematology. About one in four patients is still at risk for developing PTS after adequate treatment with anticoagulation and compression stockings.

The CaVenT (Catheter-Directed Thrombolysis for Acute Iliofemoral Deep Vein Thrombosis) trial provides prospective, randomized data on CDT, and is unique in that it focuses on functional rather than surrogate outcomes used in previous trials and case series, Dr. Sandset said at a press briefing in which he discussed the findings.

Still, the study is small and unlikely to change practice or resolve the controversy that has surrounded the use of early fibrinolysis since systemic thrombolytic therapy was introduced.

"For the first time, we have the evidence to support this type of treatment in centers that have access to it, but I also believe we need further study," said Dr. Sandset, a professor in the division of specialized medicine and surgery at Oslo University.

'CDT should be considered in patients with acute iliofemoral DVT and no apparent risk of bleeding.'

DR. SANDSET

Briefing moderator Dr. Charles Abrams, associate chief of hematology-oncology at the University of Pennsylvania in Philadelphia, said CaVenT provides the best randomized data to date, but that many clinicians, particularly in the United States, have been hesitant to adopt early fibrinolysis because of the increased risk of serious bleeding.

"This is a tantalizing trial, but I don't think ... when I'm back at my own institution that the next patient I see with a deep vein thrombosis is probably going to get it," Dr. Abrams said.

Results are still to come from the ongoing phase III, randomized ATTRACT trial evaluating CDT with blood-thinning drugs in 692 patients with proximal DVT. The cohort is three times larger than that of the CaVenT trial, but results from the North American trial are not expected until 2015.

CaVenT randomized 209 patients at 20 hospitals in Norway with their first acute iliofemoral DVT and symptoms for less than 21 days to CDT with alteplase (Activase) followed by standard treatment or to standard treatment alone. In all, 189 patients were evaluable for analysis. Their average age was 51.5 years (range 18-75 years), and 36% were women.

CDT significantly increased the rate of iliofemoral patency at 6 months from 47.4% with standard therapy to 65.9% ($P = .012$), Dr. Sandset said.

Importantly, patients who regained iliofemoral patency at 6 months had significantly less PTS at 2 years than those who experienced insufficient recanalization (36.9% vs. 61.3%, P less than .001). In all, 80 of the 90 patients in the CDT arm had successful lysis.

Bleeding complications were reported in 20 patients in the CDT arm and none in the control arm. Five bleeding events were clinically relevant and three were major, including compartment syndrome of the calf requiring surgery, abdominal wall hematoma requiring transfusion, and an inguinal puncture site hematoma.

No deaths, pulmonary embolisms, strokes, or other complications with a permanently reduced outcome were reported, Dr. Sandset said.

"CDT should be considered in patients with acute iliofemoral DVT and no apparent risk of bleeding," he said, adding that the results should be taken into account when guidelines are revised.

One of the problems for clinicians managing patients with DVT is that PTS can vary from simple heaviness in the leg to a constantly swollen leg that can impair the patient's ability to walk or hold a steady job, Dr. Abrams said.

"Patients with bigger clots and clots higher up in their thigh get more persistent symptoms, but you really can't predict all that well who will have a bad long-term complication," he said in an interview. "And the downside of this is that the administration of this drug in other trials has led to bleeding complications in 5% of patients, and 2% of that 5% are either strokes or retroperitoneal bleeding."

Dr. Abrams noted that older patients are also at greater risk of a bleeding complication than younger patients, and that clinicians will have to weigh the pros and cons of the current findings in this context.

Dr. Sandset and Dr. Abrams reported no conflicts of interest. ■

Ablation for Atrial Fib: Surgical Beats Catheter

BY BRUCE JANCIN
Elsevier Global Medical News

ORLANDO – Minimally invasive surgical ablation for atrial fibrillation that is refractory to antiarrhythmic agents was significantly more effective than catheter ablation in the first-ever randomized trial comparing the two therapies.

The higher rate of freedom from left atrial arrhythmia that was achieved surgically came at a cost of more procedural complications, most of which were managed conservatively and without prolongation of hospitalization.

The clinical trial was conducted at two European medical centers. It involved 124 patients with drug-refractory paroxysmal or persistent atrial fibrillation (AF) who were deemed to be at high risk of having an unsuccessful catheter ablation procedure.

Two-thirds of participants were judged high risk because they had experienced a return of their AF after a prior catheter ablation, whereas the remaining patients were considered at high risk for an unsuccessful catheter ablation because of left atrial enlargement and hypertension, Dr. Lucas V.A. Boersma explained when presenting the results of the FAST (Ablation or Surgery for Atrial Fibrillation Treatment) trial at the annual meeting of the American Heart Association.

Patients were randomized to pulmonary vein isolation by catheter ablation or to a video-assisted thoracoscopic surgical ablation procedure pioneered at the University of Cincinnati (J. Thorac. Cardiovasc. Surg. 2005;130:797-802). Surgical ablation was performed under general anesthesia, but unlike catheter ablation it did not include fluoroscopy, noted Dr. Boersma, a cardiologist at St. Antonius Hospital, Nieuwegein, the Netherlands.

The primary efficacy end point was freedom from left atrial arrhythmia lasting longer than 30 seconds without antiarrhythmic drugs at 12 months post procedure; this was achieved in 66% of the surgical ablation group, compared with 37% of the catheter ablation group.

Adverse events occurred during the 12 months of follow-up in 34% of the surgical group, compared with 16% of the catheter ablation group. Most of the adverse events in the surgical group were procedural complications, consisting mainly of pneumothorax and bleeding.

Freedom from atrial fibrillation was achieved in 66% with surgical ablation vs. 37% with catheter ablation.

DR. BOERSMA

Discussant Dr. A. Marc Gillinov, a cardiac surgeon at the Cleveland Clinic, praised FAST as a well-designed, clearly focused study with important clinical implications, given that roughly one-fourth of Americans will eventually develop AF.

"The clear inference from this trial is that if catheter ablation fails and a patient comes to me, I will say to that patient, 'We have many options, but we now have data to suggest we should discuss surgical ablation as one of those options because if you've had a catheter ablation and it failed, surgical ablation has a good chance of restoring you to sinus rhythm," he said.

"Most of the excess morbidity was related to chest drainage: retained fluid or air. I think it's reasonable to state that those complications are not major and are probably preventable," the surgeon added.

The FAST trial was funded by St. Antonius Hospital and the University of Barcelona Thorax Institute. Dr. Boersma disclosed that he has served as a consultant to Medtronic, and Dr. Gillinov is a consultant to Edwards Lifesciences and AtriCure.

Concurrently with Dr. Boersma's presentation at the American Heart Association meeting, the FAST results were published in Circulation (doi:10.1161/CIRCULATIONAHA.111.074047). ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: The FAST trial is one of the few randomized controlled trials of thoracoscopic surgical ablation and the only one to compare this surgical technique to catheter ablation. A total of 124 patients who had either failed prior catheter ablation or were at high risk for failure because of a large atrium with hypertension were randomized to surgical or catheter treatment. The results convincingly show that in this group of "difficult" atrial fibrillation patients, the surgical ablation approach is more effective, although there is more acute morbidity with this approach. With these data, it is reasonable to consider proceeding to minimally invasive surgical ablation in experienced centers should catheter ablation fail to maintain sinus rhythm.

Ultrasound Thrombolysis a Quick Clot Buster

BY KERRI WACHTER
Elsevier Global Medical News

NEW YORK – Ultrasound-accelerated thrombolysis treatment of submassive pulmonary embolism reduced right ventricular dilatation and the risk of heart failure, according to the results of a retrospective study of 29 patients at one facility.

"My end point is not so much seeing 100% clot clearance. My main goal of therapy is to see that regression of the right ventricle. We want to see that [right ventricle/left ventricle] ratio go back to normal to prevent long-term sequelae," explained Dr. Tod C. Engelhardt, who presented the study results at the Veith Symposium on Vascular Medicine sponsored by the Cleveland Clinic.

Dr. Engelhardt and his colleagues found that ultrasound-accelerated thrombolysis (USAT) significantly reduced the right ventricle/left ventricle (RV/LV) ratio from 1.37 to 1.02 following treatment. All patients survived to hospital discharge, with a median time to follow-up CT of less than 48 hours. Symptoms such as dyspnea and difficulty speaking resolved 2-3 hours after the initiation of treatment.

"This is an interesting group because when they present, they don't look too bad on paper or clinically," he said. These patients usually have normal blood pressure with minimal oxygen supplementation, but more than 90% have some dyspnea with exertion. About 40% of patients with PE have the submassive type, which has a 90-day mortality of 22%, compared with 58% for massive PE.

"The thing that separates them is right ventricular enlargement. They have impending right heart failure because of the right ventricular dilatation." An RV/LV ratio greater than 0.9 is considered significant, noted Dr. Engelhardt, chair of cardiovascular and thoracic surgery at East Jefferson General Hospital in Metairie, La.

Patients with persistent RV dysfunction at discharge are approximately eight times more likely to have recurrent PE and four times more likely to die, compared with patients in whom RV dysfunction had regressed by the time of discharge.

"There has to be a high index of suspicion of PE," he said in an interview. Usually the emergency physician will have chest computed tomographic angiography (CTA) done. "Once you get the scan, you can see the PE and the right heart size. Then I get an echocardiogram and a duplex scan of the lower extremities" to look for deep vein thrombosis.

However, "I have found that the CTA gives me everything that I need in order to make a decision and to proceed with therapy. The CTA does two things for me. I can see the extent of the involvement of the pulmonary embolism, and I can measure the relative sizes of the right and left ventricles to generate that ratio. This allows me to categorize the patient as a submassive PE patient and to move forward with therapy," he said.

Once the diagnosis of PE is made, the patient is started on anticoagulant therapy. "I don't think that hinders what I do; in fact, it complements it."

With a patient with a submassive pulmonary embolism, "once I make the diagnosis and the patient is already anticoagulated, my next step is to move to the cath lab to place catheters and start [USAT] treatment."

With USAT, ultrasound energy causes fibrin strands to thin and loosen,

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Ultrasound-accelerated thrombolysis represents an advancement in the treatment of pulmonary embolism. In this single-center study, there was no intracranial or systemic bleeding with the reduced dose of thrombolytic combined with USAT. Larger ongoing trials are underway to evaluate harder end points of this modality. If found to improve survival and lower health care costs, this will represent a major shift in the treatment of pulmonary embolism.

exposing plasminogen receptor sites. Thrombus permeability and thrombolytic penetration are dramatically increased. Ultrasonic pressure waves force the thrombolytic deep into the clot, allowing the drug to work faster and clear the clot sooner with a lower drug dose and without hemolysis.

The goal of USAT is to accelerate thrombolysis and rapidly reverse right ventricular dilatation and reduce pulmonary clot burden. This improves pulmonary perfusion and reduces right heart load. Because a lower drug dose (no more than 20 mg of recombinant tissue plasminogen activator [TPA]) is used than with conventional treatment, the risk of bleeding is significantly lowered.

Aggressive management of submassive PE can prevent more harmful consequences later, according to Dr. Engelhardt.

Dr. Engelhardt reported on the experience at his center, where surgeons treated 32 PE patients with ultrasound-accelerated thrombolysis between February 2009 and June 2011.

They performed retrospective data analysis on 29 consecutive patients with pre- and posttreatment contrast-enhanced CT imaging, clinical history, RV/LV ratio reduction, and clot burden reduction. They used this information to identify the optimum drug dose as a maximum of 20 mg recombinant TPA over 12 hours. This dose resulted in good clinical outcomes with no bleeding complications.

Adverse effects were limited. There were no intracranial hemorrhages or systemic bleeding complications. Four patients had puncture site bleeding that required transfusion. One patient had suspected recurrent PE.

Although there has been "trepidation in changing the status quo of anticoagulation alone," he said, "patients with massive and submassive emboli can be treated with USAT. Certainly patients who are in cardiogenic shock may have time for a catheter placement and can be treated with systemic TPA. Many massive PE patients can be resuscitated so that they do have time for catheter placement."

The catheters are inserted over a 0.35-inch guidewire through the femoral vein. "When I first started doing this – the first 10 or so patients – I did bilateral groin sticks because I'm placing bilateral pulmonary artery catheters," said Dr. Engelhardt.

He now uses a 10-French catheter that has two ports. "So I can now put catheters in each port and feed one into the right and one into the left." The catheter includes small ultrasound transducers and allows for thrombolytic drug delivery.

AGGRESSIVE MANAGEMENT OF SUBMASSIVE PULMONARY EMBOLISM CAN PREVENT MORE HARMFUL CONSEQUENCES LATER.

"I developed a protocol when I first started doing these cases. I was giving a bolus dose down each side – 4 mg each side – then I would run it for 12 hours at 0.5 mg per side. Since then, I've decided not to give a bolus dose but to run 0.5 mg per side for 20 hours," he said.

He now administers 20 mg total because he found that larger doses provide the same results as 20 mg but with complications such as groin hematomas.

"These catheters treat only what they're in contact with, so I try to get these catheters as far into the periphery of the lung as I can. I've never had a perforation," he said.

Dr. Engelhardt is a consultant to EKOS Corp., which makes the ultrasound device. ■

CHRISTINA CHAMBERS, PH.D., M.P.H.

COMMENTARY

Asthma Drugs in Pregnancy

Asthma continues to be one of the most common chronic conditions complicating pregnancy; approximately 8% of pregnant women in the United States report a current diagnosis. Asthmatic women are at increased risk of adverse birth outcomes and perinatal complications, including spontaneous abortion, preterm delivery, reduced birth weight, preeclampsia, and in selected studies, congenital anomalies. In some cases, these increased risks have been linked to specific medications (for example, oral corticosteroids and orofacial clefts). But much of the current evidence is also consistent with the interpretation that at least some of the excess risk can be attributed to the underlying severity and/or inadequate control of maternal asthma.

However, two recently published studies suggest that beta$_2$-agonists – mainstays of treatment and control of asthma symptoms – may be associated with increased risks of congenital anomalies.

The first, an analysis conducted with data from the National Birth Defects Prevention Study, focused specifically on orofacial clefts as the outcome and bronchodilators as the exposure. Using a case control design, 2,711 mothers of infants with oral clefts and 6,482 mothers of infants with no malformations in 10 states were interviewed between 1997 and 2005 about bronchodilator use for asthma during and just before pregnancy. The authors separately evaluated risks for cleft lip alone, cleft lip with cleft palate, and cleft palate alone, as each of these defect categories may have distinct etiologies. Almost 3% (247 women) reported exposure to any bronchodilator in the periconceptional period, with nearly 90% of those exposures limited to the widely used short-acting beta$_2$-agonist, albuterol.

Significantly increased risks were noted for any bronchodilator use (without an additional anti-inflammatory drug) and cleft lip alone (adjusted odds ratio, 1.77; 95% confidence interval, 1.08-2.88); however, with the addition of an anti-inflammatory drug (four cases), the odds were attenuated and no longer statistically significant.

Limiting the analysis to only those reporting use of albuterol, the estimated risks for cleft lip alone (adjusted OR, 1.79; 95% CI, 1.07-2.99) and cleft palate alone (adjusted OR, 1.65; 95% CI, 1.06-2.58) were both significantly elevated.

No increased risks were noted for use of any bronchodilator and cleft lip with cleft palate. If these findings represent a causal association, the estimated odds ratios would translate to less than one excess case each of cleft lip alone and cleft palate alone for every 1,000 women using albuterol in the first trimester (Hum. Reprod. 2011;26:3147-54).

As the authors pointed out, there was no mechanism in the study to adjust for the contribution of

Continued on following page

Pregnancy Outcomes Not Marred by 2009 Flu Pandemic

'There did not appear to be any significant differences in pregnancy outcomes between cases and controls.'

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO – H1N1 influenza infection during the 2009 pandemic did not impact pregnancy outcomes in a retrospective cohort study of 887 women.

Subtle differences were observed, however, among women with severe infection or delayed treatment, Dr. Amber Naresh reported at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

She presented a retrospective cohort study performed at three tertiary care medical centers of all inpatient and outpatient cases of pregnant women with laboratory-confirmed 2009 H1N1 influenza.

For each case, five pregnant women who tested negative for H1N1 influenza or were untested were randomly chosen from each site's database and matched by estimated date of confinement and site.

Based on a preliminary analysis, the 147 H1N1 cases and 740 controls had nearly identical birth weights (average 3,208 g vs. 3,219 g) and gestational ages at delivery (average 38.5 vs. 38.7 weeks).

After the investigators controlled for study site, age, race, multiples, primiparity, medical conditions, and smoking, the cases and controls also had similar rates of the following:

- Term low birth weight (5.6% vs. 3.6%; odds ratio, 1.45).
- Preterm delivery less than 37 weeks' gestation (13.3% vs. 11.6%; OR, 1.10).
- Premature rupture of membranes (1.7% vs. 2.6%; OR, 0.61).
- Abruption (0.9% vs. 1.2%; OR, 0.49).
- Cesarean section (27.5% vs. 30%; OR, 0.82).
- Induction (36% vs. 39%; OR, 0.83).
- Fetal anomalies (4.7% vs. 4.9%; OR, 1.24).
- Hypertensive disorders of pregnancy (14.3% vs. 13.2%; OR, 0.98).
- Neonatal ICU admission (13% vs. 11%; OR, 1.21).

"There did not appear to be any significant differences in pregnancy outcomes between cases and controls," said Dr. Naresh of Magee-Women's Hospital of the University of Pittsburgh.

Pregnancy outcomes also did not differ when stratified by trimester, although more infections occurred in the second trimester, followed by the third and first trimesters, she said.

Previous case series have suggested an increased rate of preterm delivery, reaching 30% in an early report of H1N1 influenza in pregnancy and 60% among critically ill women.

A recent study also reported lower birth weights among 16 women with proven H1N1 infection, compared with 25 women with influenzalike illness (Am. J. Obstet. Gynecol. 2011;204[suppl. 1]:S58-63), she said.

A subgroup analysis of women in the current study with severe disease, defined as requiring hospitalization, identified a nonsignificant trend for lower birth weight, compared with controls (3,013 g vs. 3,219 g), and lower gestational age (37.9 weeks vs. 38.7 weeks).

The combined outcome of term low birth weight, preterm birth, and abruption was significantly more common among the severe H1N1 cases than controls after study site, age, race, multiples, primiparity, medical conditions, and smoking were controlled for (31.4% vs. 15.7%; OR, 2.45).

In addition, more than 30% of women in the severe group had complications, compared with only 15% in the control group, Dr. Naresh said.

The researchers also looked at the influence of early antiviral administration, which has been reported to be associated with fewer maternal ICU admissions and fewer deaths (JAMA 2010; 303:1517-25).

Gestational age at delivery was 1 week earlier among the 27 women receiving oseltamivir (Tamiflu) more than 48 hours after symptom onset, compared with the 52 women receiving it in less than 48 hours, as recommended by the manufacturer (37.6 weeks vs. 38.6 weeks).

"It's not clear how clinically significant that is, but it's interesting nonetheless," Dr. Naresh said.

Birth weights among the delayed- and early-treatment groups were similar at 3,007 g and 3,160 g.

All cases of H1N1 infection were significantly more likely than controls to be black (27% vs. 19%), and to have prepregnancy diabetes (4% vs. 1%), seizure disorder (3.4% vs. 0.8%), and asthma (17% vs. 9%). The average age of the cohort was 28 years.

Limitations of the study are that some of the controls may have had influenza since many were untested and that data on specific neonatal outcomes associated with ICU admission were limited.

Dr. Naresh said future steps include a small-for-gestational-age analysis and an evaluation of the role of socioeconomic status and of differences among the three sites: the University of Pittsburgh Medical Center, the University of Colorado at Denver, and the University of Washington Medical Center in Seattle. ■

VITALS

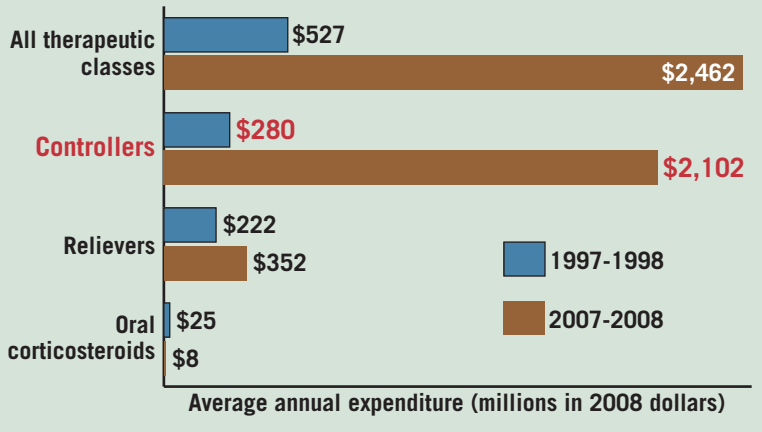
Major Finding: Cases and controls had nearly identical birth weights (3,208 g vs. 3,219 g) and gestational ages at delivery (38.5 weeks vs. 38.7 weeks).

Data Source: Retrospective cohort analysis of 147 pregnant patients with 2009 H1N1 influenza and 740 pregnant controls.

Disclosures: Dr. Naresh and her coauthors reported no relevant financial disclosures.

DATA WATCH

Annual Spending on Asthma Controllers for Children Rose 651% From 1997-1998 to 2007-2008



Note: Based on data from the Medical Expenditure Panel Survey.
Source: Agency for Healthcare Research and Quality

ELSEVIER GLOBAL MEDICAL NEWS

Continued from previous page

underlying disease severity and/or asthma symptom control in these mothers. However, the lack of an association between orofacial clefts and bronchodilators among those women who also used an anti-inflammatory drug suggests that perhaps women on polytherapy had more optimum treatment and therefore better control.

The second study used a retrospective cohort design drawing on administrative data collected between 1990 and 2002 in Quebec. The 13,117 pregnancies selected for the analysis were limited to those with a coded diagnosis of asthma and excluded women who received multiple prescriptions for oral corticosteroids in the year before pregnancy.

The exposures evaluated were any prescription in the periconceptional period for a short-acting beta$_2$-agonist rescue medication (such as albuterol), and any prescription in the periconceptional period for a long-acting beta$_2$-agonist controller medication (such as salmeterol, available during the years of this study as a single active ingredient medication).

In all, 17 categories of major congenital malformations were evaluated as outcomes, including orofacial clefts. More than 50% of pregnant women in the study filled a prescription for a short-acting drug in the first trimester, while only 1.3% received a prescription for one of the long-acting medications.

The authors found no significant associations with short-acting beta$_2$-agonists for any of the congenital defect categories. Cases of cleft lip and cleft palate were combined, and the odds ratio after considering adjustment factors was 1.50 (95% CI, 0.72-3.14).

However, the authors did report that first-trimester prescription for long-acting beta$_2$-agonists was associated with significantly increased risks for major cardiac malformations (adjusted OR, 2.30; 95% CI, 1.11-5.10) based on seven infants exposed and "other or unspecified major malformations" (adjusted OR, 3.97; 95% CI, 1.29-12.20) based on three infants exposed (Birth Defects Res. Clin. Molec. Teratol. 2011;91:937-47). In this study, the authors attempted to control for underlying disease severity using Canadian treatment guidelines as well as emergency department and other hospital admissions for asthma.

However, no direct measure of disease severity or symptom control was collected, and unfortunately, the "lumping" of orofacial clefts (likely due to the small number of affected infants) makes comparison to the above-described study difficult. The findings with long-acting beta$_2$-agonists, as the authors point out, could be influenced by the higher rate of more severe and less well-controlled asthma among these women, the expected higher rate of preterm delivery with associated prematurity-related defects, and/or multiple testing/chance. Finally, it has been suggested that some asthmatic women will reduce or discontinue medication in the first trimester of pregnancy based on fear of fetal exposure, not on remission of symptoms. If in fact this is the case, prescriptions filled may not reflect true usage of the drug.

EVEN SMALL INCREASED RISKS FOR ASTHMA MEDICATIONS DURING PREGNANCY CAN FURTHER DETER WOMEN FROM APPROPRIATE TREATMENT.

With respect to previously published studies, an increased risk for congenital anomalies in general or orofacial clefts in particular, has not been suggested for albuterol. There is a lack of published data on long-acting beta$_2$-agonists and pregnancy outcome. Thus, although neither of the two new studies reviewed above will likely change clinical practice, they both point out the need for further study of commonly used asthma medications and, specifically, studies that incorporate direct measures of disease severity and/or symptom control. Reports of even small increased risks for asthma medications during pregnancy can further deter women from appropriate treatment, which in turn may result in unintended risks for both mother and baby. ■

DR. CHAMBERS *is associate professor of pediatrics and family and preventive medicine at the University of California, San Diego. She is director of the California Teratogen Information Service and Clinical Research Program. Dr. Chambers is a past president of the Organization of Teratology Information Specialists and past president of the Teratology Society. She said she had no relevant financial disclosures.*

New COPD Treatments Being Developed

BY DOUG BRUNK
Elsevier Global Medical News

HONOLULU – Current interventions for chronic obstructive pulmonary disease leave many patients with unmet needs, said Dr. Nicola A. Hanania, FCCP.

"We know from large clinical trials that current pharmacotherapies do not change the natural history of COPD, and many patients remain symptomatic with current therapies," Dr. Hanania, director of the asthma clinical research center at Baylor College of Medicine, Houston, said at the annual meeting of the American College of Chest Physicians.

Inadequate adherence to therapy "is a major cause of poor clinical outcomes in the treatment of COPD," he said. The cost, compliance, and safety of certain agents are issues "that we cannot ignore."

When considering a therapy for COPD, clinicians should factor in components of COPD beyond bronchoconstriction, he advised, including mucociliary dysfunction, structural changes in the airway and the lung, systemic components, and airway inflammation. "We also have to look at outcomes other than lung function including exacerbations, activity limitation, and symptoms of dyspnea," he said. "We are no more satisfied with just a drug that improves lung function but does nothing for the patient-reported outcomes."

Dr. Hanania's "wish list" for an ideal COPD therapeutic option in the future is one that addresses the multiple components and phenotypes of COPD. He said he would like to see drugs that blunt proinflammatory cells and molecules known to be involved in COPD. Agents should be well tolerated and compatible with other therapies for COPD and comorbid conditions, be simple to administer, and have the potential to improve patient adherence, he added.

Treatment approaches being studied include novel formulations of existing medications, such as the combination of ultralong-acting beta$_2$ agonists and long-acting antimuscarinics. Other agents in "development include bifunctional muscarinic antagonist–beta$_2$-agonists and combinations of once-daily long-acting beta$_2$-agonists and inhaled corticosteroids.

However, perhaps the most promising pharmacotherapies will be novel agents aimed at reducing local and systemic inflammation. "We know that COPD is an inflammatory disease, so we need drugs that can target inflammation right from the very beginning," Dr. Hanania explained. "Inhaled steroids are important, but they're not as effective in COPD as they are in asthma."

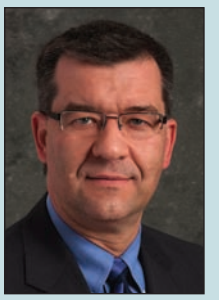
Phosphodiesterase type 4 inhibitors are currently being studied in COPD. These agents reduce the activity of neutrophils, macrophages, and CD8-positive T lymphocytes, as well as the expression of cytokines and other inflammatory mediators. Currently, the only phosphodiesterase type 4 inhibitor approved in the United States for use in patients with COPD is roflumilast (Daliresp). Several others are in development.

Because they target airway inflammation, p38 mitogen-activated protein kinase inhibitors are also being studied in COPD patients. However, so far clinical trials have found potential problems related to systemic side effects and toxicity, "indicating that it is probably necessary to deliver these drugs by inhalation to reduce systemic exposure," Dr. Hanania said.

He concluded his presentation by noting that certain medications used to treat comorbidities in COPD may have beneficial effects on COPD outcomes. These include statins, ACE inhibitors, beta-blockers, peroxisome proliferator–activated receptor agonists, and macrolides. The National Heart, Lung, and Blood Institute COPD Clinical Research Network is currently conducting a prospective randomized controlled trial in 1,126 patients with severe COPD randomized to daily simvastatin (40 mg) vs. placebo for at least 1 year. Furthermore, a recent study showed that daily azithromycin significantly reduced exacerbations in high-risk patients.

Dr. Hanania disclosed that he has received funds from the National Institutes of Health, the American Lung Association, GlaxoSmithKline, Boehringer Ingelheim, Sunovion, Novartis, Pfizer, Forest Pharmaceuticals, Dey Pharmaceuticals, and AstraZeneca. ■

COMMENTARY



Dr. Darcy Marciniuk, FCCP, comments: COPD has recently overtaken stroke to become the third leading cause of death in the United States, and barriers to optimal clinical care are abundant. Our patients continue to suffer. But as outlined by Dr. Hanania, many new potential therapies are being investigated – there are reasons to be hopeful the future holds exciting breakthroughs in COPD management.

IOM Calls for Research on E-Cigs, Tobacco Lozenges

BY JANE ANDERSON
Elsevier Global Medical News

Modified-risk tobacco products – such as e-cigarettes and tobacco lozenges that may reduce the health risks of using tobacco – could represent part of a comprehensive strategy to combat tobacco-related disease and death, but too little is known about whether they actually pose less risk than do traditional tobacco products, according to a report issued by the Institute of Medicine.

Consequently, the Food and Drug Administration should require specific types of research on these modified-risk products before allowing tobacco companies to sell or advertise them as being capable of reducing the health effects of tobacco use, the IOM report recommended.

The research should determine whether the product really presents a lessened risk for a person who might use it, Dr. Jane Henney, committee chair and professor of medicine and public health sciences at the University of Cincinnati, said in an interview. The product "also should not negatively impact the general public, as in the case of secondhand smoke, and it shouldn't raise the risk" for nonusers or former users to begin or resume using the product.

Few smokers – only about 6% each year – are able to successfully quit tobacco use. Because quitting is so difficult, many cigarette smokers would welcome products that allow them to continue smoking with less risk to their health. However, there's no research showing that modified-risk tobacco products are safer; in fact, so-called "light" cigarettes actually turned out to be just as risky as regular cigarettes, the IOM report said.

The Family Smoking Prevention and Control Act of 2009 gave the FDA the authority to ensure that modified-risk tobacco products actually do reduce tobacco-related harm before they can be marketed. The 2009 law also directed the IOM to work with the FDA on the design and conduct of scientific studies of modified-risk tobacco products.

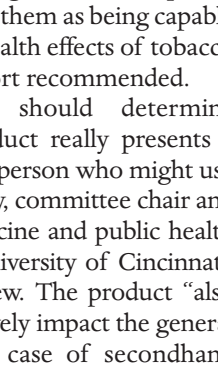
The tobacco industry "is new to regulation, and has a past history that would lead one to believe it can't be trustworthy," Dr. Henney said. "We speak to the governance tools that should be put in place to really open up this process."

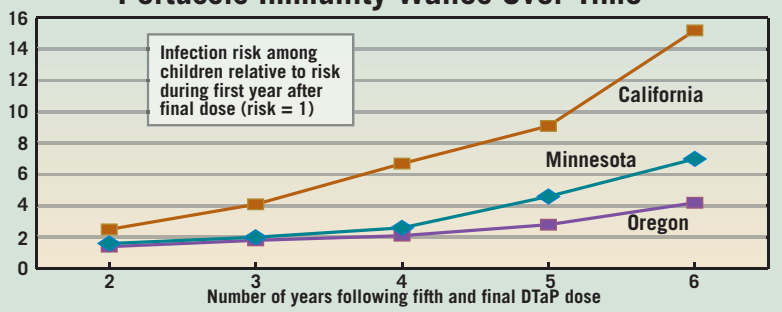
In part because of this trust gap, companies and other sponsors who develop modified-risk tobacco products should consider using FDA-approved, independent third parties to oversee health and safety research on their product, the IOM recommended. Independent oversight would ensure that data submitted to the FDA are reliable and credible and might help lure institutions and scientists back into the field; currently, many refuse to conduct or publish research supported by the tobacco industry. Tobacco makers now lack the capacity and expertise to conduct valid scientific research on their own products, according to the report.

The report recommends that studies on modified-risk tobacco products should examine the product's composition and addiction potential, the amount of human exposure to harmful components, perceptions about the product's effects and likelihood of addiction, and its effects on human health. Studies should be "generalizable" to the whole population, but also should include populations of special relevance, including current and former smokers, beginning smokers, adolescents, and populations at high risk for tobacco use. ■

COMMENTARY

Dr. Vera DePalo, FCCP, comments: Tobacco use is a major risk factor for disease and has been identified as a leading cause of preventable death. In most cases, individuals start smoking at a young age, and the process of cessation is often long, requiring several attempts. Smokers reach to many products to reduce their dependence on cigarettes. Knowledge of safety and efficacy is crucial in making an informed choice. Research is necessary to inform choice.





Note: Based on data for 682 pertussis cases and 2,016 controls (Calif.), 521 cases and 224,378 controls (Minn.), and 99 cases and 179,011 controls (Ore.).
Source: Dr. Tartof

After Final Dose, Risk Rises

Vaccine • *from page 1*

greater vulnerability in 7- to 10-year-olds," commented Dr. Kathryn M. Edwards, director of the Vaccine Research Program at Vanderbilt University, Nashville, Tenn.

"The durability of protection with the acellular vaccine is not as good as with the whole-cell vaccine, but the problem with the whole-cell vaccine was that it was quite reactive," causing fevers and local reactions, she said in an interview.

"At this point, people would not accept the whole-cell vaccine," she said. Possible options include additional boosted vaccinations, or moving administration of the fifth childhood dose of DTaP from age 4 to age 6. The CDC's recommended vaccination schedule already calls for delivery of the fifth dose at ages 4-6 years, but in reality most U.S. children receive it at age 4 when they enter preschool.

One of the CDC studies focused on pertussis cases that appeared in any of 15 California counties during the state's 2010 epidemic. Chart reviews by CDC researchers identified 682 pertussis cases among children aged 4-10 years, and 2,016 unmatched controls from the same age group and counties. Roughly 70% of the children who had received all five scheduled doses had received their fifth dose at 4 years, and about 30% received their fifth dose at 5 years.

An analysis of the time elapsed following the fifth dose relative to when pertussis infection occurred showed that after 5 years the vaccine efficacy was 71% below where it stood immediately after the fifth dose, reported Lara K. Misegades, Ph.D., an epidemic intelligence officer also with the CDC's National Center for Immunization and Respiratory Diseases.

This translated into a 15-fold higher relative risk for infection in children during the sixth year following their final dose, compared with the first 12 months after their fifth dose, Dr. Tartof said.

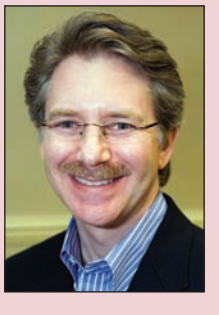
The second CDC study, presented by Dr. Tartof, used data collected by immunization registries and reports to the CDC through the National Notifiable Disease Surveillance System. This analysis included 224,378 fully immunized children and 521 pertussis cases in Minnesota, and 179,011 fully immunized children and 99 reported cases in Oregon.

Dr. Tartof and her associates used these data to calculate a pertussis incidence rate during each year following delivery of the fifth childhood dose, and the relative risk for infection during each follow-up year relative to the first 12 months after the fifth dose. The risk for infection rose steadily during each year following the fifth dose. (See table.)

Dr. Tartof, Dr. Edwards, and Dr. Misegades had no relevant disclosures. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: The failure of acelluar pertussis vaccine, and the corresponding lack of herd immunity, presents a problem for patients of all ages. As the prevalence of pertussis increases in a population with waning immunity, we must be prepared for more disease in formerly atypical age groups.



FDA Approves Ventricular Assist Device for Children

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

The long-awaited "Berlin Heart," a ventricular assist device for infants and children with heart failure, has been approved in the United States.

The mechanical pulsatile cardiac assist device, which comes in different sizes to fit children from newborns to teenagers, was approved by the Food and Drug Administration on Dec. 16.

"Previous adult heart assist devices were too large to be used in critically ill children to keep them alive while they wait to get a new heart," Dr. Susan Cummins, chief pediatric medical officer in the FDA's Center for Devices and Radiological Health, said in the statement.

The device, commonly referred to as the Berlin Heart, is the EXCOR Pediatric System, and is manufactured by Berlin Heart, a German company. The device consists of one or two external pneumatic blood pumps, tubes to connect these pumps to the chambers of the heart and the great arteries, and a driving unit, according to the FDA.

Use of the EXCOR device improved survival to transplant among patients in a U.S. study of 48 pediatric patients, compared with those treated with the current standard of care, extracorporeal membrane oxygenation (ECMO), the agency statement said. Stroke is a risk associated with use of the EXCOR device.

It was approved under a Humanitarian Device Exemption, which requires proof that "the probable benefit from use of the device outweighs the probable risk of illness or injury from its use to obtain the FDA's approval," the agency said.

One of the study sites was Texas Children's Hospital, Houston. In a statement released by the hospital, Dr. Charles D. Fraser Jr., the hospital's surgeon in chief, said that the approval "ushers in a new era for children with terminal heart failure. The medical community is now able to offer this life-saving device to support desperate children who would not otherwise survive while awaiting donor hearts."

Because of the small number of pediatric-size donor hearts available, the median wait time for a donor heart for infants is 119 days; 12%-17% of children and 23% of infants on heart transplant lists die before a heart becomes available, according to the FDA. ■

The EXCOR Pediatric System, commonly called the Berlin Heart, consists of one or two external pneumatic blood pumps, tubes to connect these pumps to the chambers of the heart and the great arteries, and a driving unit.

IMAGES COURTESY BERLIN HEART INC.

COMMENTARY

Dr. Susan Millard, FCCP, comments: This new development gives hope for the families and children with end-stage heart failure who are now awaiting transplant. I applaud the researchers for thinking "outside of the box," as the adult heart assist devices were too large. This development exemplifies the statement that "kids should not be treated like little adults."

COMMENTARY

Medicaid Primer 2012: Avoiding the RAC

All legislation passed by our government has seemingly good intentions, and so it goes with the Affordable Care Act. However, with all legislation comes unintended consequences, and this has proven true with the ACA.

Tucked into the reams of legislation were provisions for tightening antifraud and abuse efforts in state Medicaid programs via the Recovery Audit Contractor (RAC) program. RACs are independent contractors using professionally trained coders under the authority of the Centers for Medicare and Medicaid Services (CMS). They perform focused chart audits on physician CPT coding outliers in an attempt to identify and recoup improper overpayments and underpayments made to providers. From an audit of charts, a statistical analysis is done to estimate total overpayments and the physician or group is assessed a fine. A contingency fee of up to 10% is paid to the RAC upon recovery of monies.

STUART A. COHEN, M.D., M.P.H.

I have spent many hours at the American Medical Association House of Delegates listening to physicians' complaints of arbitrary, capricious, and even egregious behavior by these RAC companies preying upon Medicare practices to collect their contingency fees. Lack of timely response to physician grievances, lack of physician oversight of the coders, systematic overestimation of overpayments and underrecognition of underpayments, and lack of due process appeal procedures are just some of the litany of complaints aired.

The RAC is akin to an IRS audit, and the financial consequences – as well as costs to one's business reputation – are to be avoided at all costs. Modest changes have been made by the CMS in response to concerns, and since 2005, the Medicare Trust Funds have recovered over a billion dollars in overpayments.

Beginning Jan. 1, permanent RAC audits will be implemented in state Medicaid programs as part of routine compliance and audit procedures, thanks to the ACA, so the RAC soon may be coming to your office.

What can you expect, and how can you avoid getting wrecked by RAC?

Based on comments from the Health and Human Services Department Office of Inspector General (OIG 2012 audit Work Plan) and past Medicare and Medicaid audits, it seems for now the low-hanging fruit is the 99214/99215, and modifier –25 outliers will be likely targeted.

It appears that initial Medicaid RAC audits by states may or may not offer sufficient due process as the auditors stumble out of the starting gates. Rules of engagement, including an appeals mechanism and timely response to physician grievances, have yet to be implemented in most states, even at this late date. Unfamiliarity with state Medicaid rules and regulations may also interfere with a smooth transition of this program into Medicaid.

On an individual level, I recommend immediately becoming familiar with the AMA CPT 2012 manual, which interprets the AMA CPT rules and regulations. Establish office consensus on your coding procedures. Document all of your work. Self-audit your level 4 and 5 E & M codes and your modifier –25s to ensure you comply with all the necessary documentation.

If you have an EMR, make sure your code level, despite enough documentation, is appropriate for the level of medical decision making. If you are in a large group, establish a coding and compliance committee that routinely does chart audits, sets group policy, and implements yearly group education on CPT coding. Create a group policy manual.

Remember, if your community codes level 99214s at an average of 24% and you are at 60%, "you've got some 'splainin' to do!"

If the community average for modifier 25s is 4% of health supervision visits and you are at 25%, you will be audited. The cost to your practice and the mental anguish to you and your staff may not be worthwhile, so consider taking a hard look at your internal billing and coding practices now.

On a macro level, I suggest several actions. First, work with your state medical society general counsel to monitor state implementation of the RAC. Ensure appropriate procedures, due process including a formal appeals mechanism, professional coders under physician oversight, timely response to provider concerns, and avoidance of flawed statistical analysis, as well as overlooking of underpayment.

Second, have your state medical society advocate for a managed care Medicaid waiver for RAC – the managed care plans already have extensive compliance and audit procedures that need not be duplicated by the RAC.

Finally, monitor the audit and compliance procedures of the commercial health plan with which you work. They often copy-cat Medicare and could perhaps view fraud and abuse recovery as a way to enhance their revenue, so implement all the above tactics with your commercial health plan patients as well.

We are entering a new milieu of CPT coding and compliance. Higher coding may not be as desirable as "more accurate" coding. Hiding below the radar by not entering CPT outlier territory may be more preferable than being a well-reimbursed CPT outlier with your office serving as a bull's eye for target practice by your friendly neighborhood state RAC auditor. ■

DR. COHEN *is in general pediatric practice and a board member of Children's Primary Care Medical Group Inc. of San Diego, and assistant professor of pediatrics at the University of California, San Diego. He is vice chair of the American Academy of Pediatrics, District 9 and president of the San Diego County Medical Society Foundation. He has represented the American Academy of Pediatrics at the American Medical Association for many years. He said he had no relevant financial disclosures.*

Starting Dates Pushed Back

ACOs • *from page 1*

"When folks see the rules and see the many changes, they will see that CMS listened," Jonathan Blum, CMS deputy administrator and director of the Center for Medicare, said during the briefing.

In the proposed rule, half of primary care physicians in an ACO had to meet the meaningful use criteria for EHRs by the second year of what will be 3-year contracts with the CMS. Under the final rule, EHRs will not be required, but instead be heavily weighted as a measure of quality of care.

The final rule also pushes back the program's starting dates. Originally, the CMS envisioned a start date of January 2012 for organizations that wanted to participate.

Now, the program will be established this month with the initial agreements starting in April or July of this year. The first performance "year" will be 18 or 21 months in length, rather than 12 months.

Under the final rule, there are two components to the ACO program: the Shared Savings Program and the Advanced Payment Model.

To be eligible to participate in the Shared Savings Program, ACOs must be able to be held accountable for at least 5,000 beneficiaries a year for each of the 3 years of the agreement. Only certain parties may sponsor an ACO: physicians in group practices, individual practitioner networks, or hospitals. That list was expanded in the final rule to include collaborations between Rural Health Clinics and Federally Qualified Health Centers.

To earn shared savings, ACO participants will have to report on measures that span four quality domains: quality standards, care coordination, preventive health, and at-risk populations. The final rule substantially reduces the number of quality measures, from 65 in five domains to 33 in four domains. In the first year, ACOs that are sharing savings only will be required to report on these measures to receive payment. In the second year, they will need to meet pay-for-performance standards on 25 of the measures, growing to 32 measures in the third year.

In the proposed rule, ACOs could share savings only in the third year of the 3-year agreement. Now, they can share beginning in the first. The CMS says this will help less-experienced organizations gain know-how before they more fully participate in the program. Fuller participation would have ACOs sharing losses, as well.

The savings-only route has ACOs splitting up to 50% of the savings with the CMS. If an ACO chooses to also share losses, it will get up to 60% of the savings. Under the proposed rule, the CMS could withhold 25% of pay-for-performance bonuses, but that has been removed from the final rule.

Also, under the proposed rule, ACOs would start sharing in the savings only after they had passed a minimum threshold set by the CMS. That threshold was established to ensure that the savings weren't just random, Dr. Berwick said. The minimum still exists under the final rule, but now, if the savings aren't just due to a random variation in costs, the ACO can share in savings starting with the first dollar, Dr. Berwick said.

The final rule made some changes to how Medicare beneficiaries would be assigned to ACOs, noting that "determination of whether an Accountable Care Organization was responsible for coordinating care for a beneficiary will be based on whether that person received most of their primary care services from the organization."

To spur participation in the Shared Savings Program, the CMS also announced that it would make money available to physicians, hospitals, and others for major capital investments under the Advanced Payment Model.

This model will pay a portion of future savings to eligible participants. Once they begin sharing in savings, they will have to repay the money. According to the final rule, eligible ACOs will either receive an upfront, fixed payment; an upfront, variable payment; or a monthly payment of varying amount depending on of the number of Medicare beneficiaries historically attributed to the ACO. More information on eligibility and requirements is at the agency's innovation center's website.

Simultaneously with the announcement of the final rule, several federal agencies issued additional guidance on how ACOs could steer clear of violating antitrust laws and other measures designed to keep medicine competitive.

The HHS Office of Inspector General also issued an interim final rule on how the ACOs could stay within the antikickback rules.

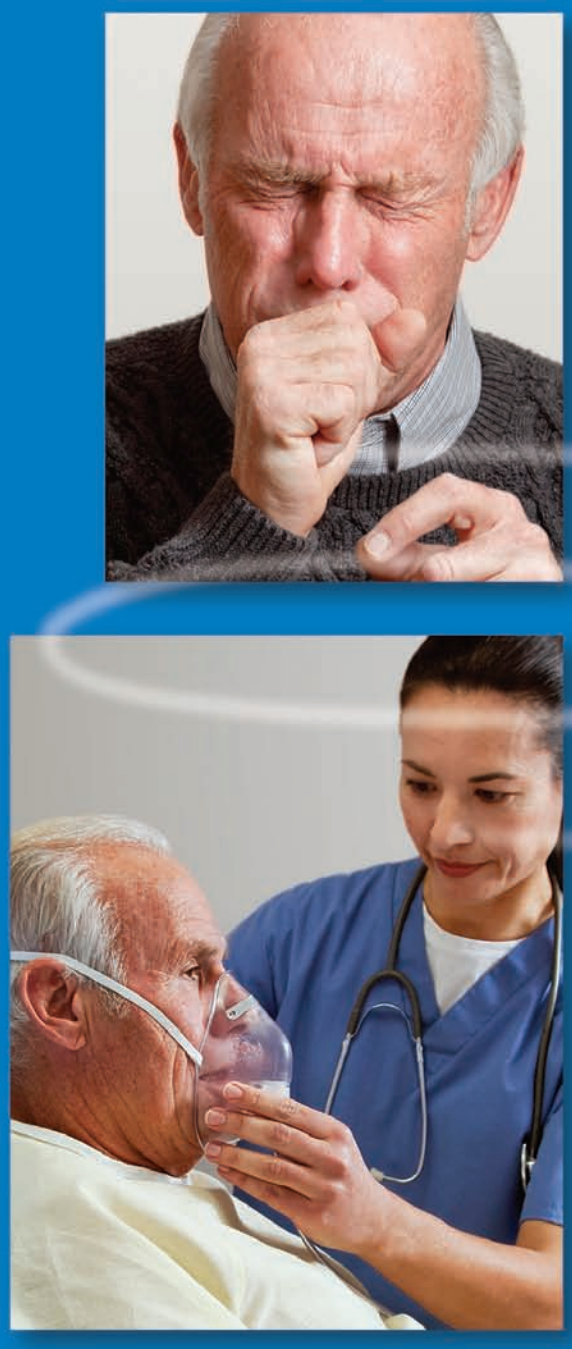
In the proposed rule, ACOs were required to seek antitrust review from the Federal Trade Commission and the Department of Justice. The final rule lifts that requirement, and instead advises potential ACOs to seek review. Those two agencies issued a final policy statement outlining enforcement plans and indicating that voluntary reviews would likely take about 90 days. ■

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

COPD EXACERBATIONS

are serious events...

Reducing Patient Risk Is Critical



INDICATIONS AND USAGE

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

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

COPD=chronic obstructive pulmonary disease.

Daliresp®
(roflumilast) tablets
500 mcg

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

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

TREAT NOW WITH DALIRESP®

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

- Reduces moderate or severe exacerbations by 17% vs placebo[1,3,4]
- Effective alone or in combination with a bronchodilator[1,3]
- Effective in older and younger patients (>65 and 40-65 years)[1,3]
- Statistically significant increase in lung function (pre-bronchodilator FEV_1) of 48 mL vs placebo[1,4]
  - DALIRESP is not a bronchodilator; this increase was not clinically significant[1,3]
- The first class of drugs approved for COPD in 25 years[2,5]

ONCE-DAILY
ORAL

Tablet shown not actual size.

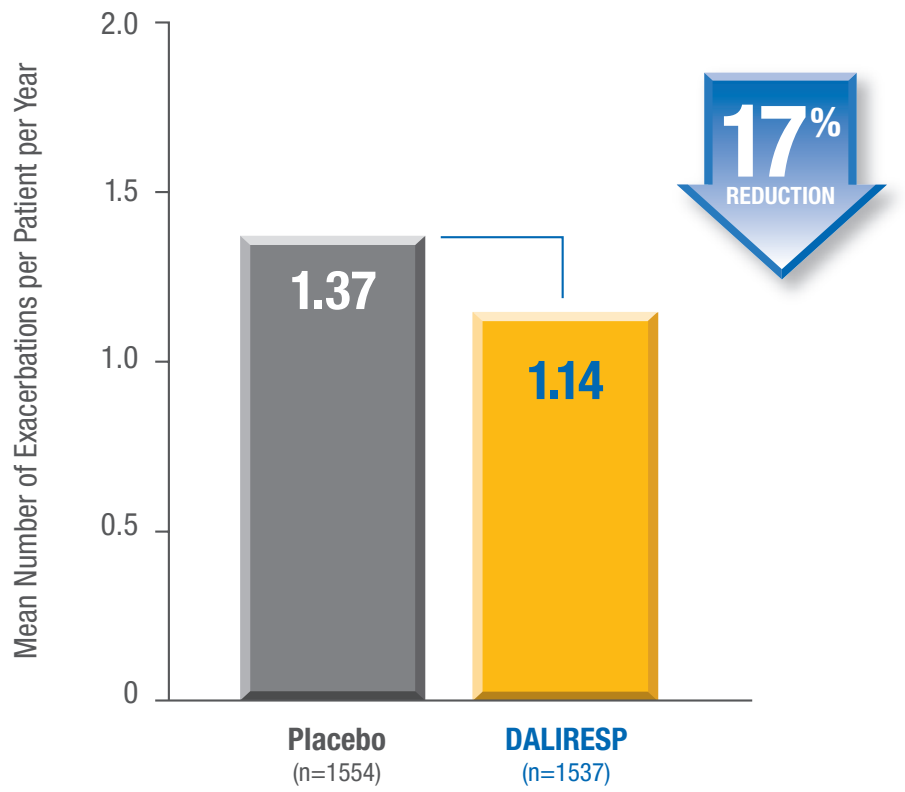
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP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

Daliresp®
(roflumilast) tablets
500 mcg

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

DALIRESP significantly reduces exacerbations

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



P=0.0003 vs placebo

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

- Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids[1]
- Severe exacerbations were defined as resulting in hospitalization and/or death[1]

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

References: 1. DALIRESP (roflumilast) Prescribing Information. Forest Pharmaceuticals, Inc. St. Louis, MO. **2.** US Food and Drug Administration. FDA approves new drug to treat chronic obstructive pulmonary disease. March 1, 2011. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm244989.htm. Accessed October 19, 2011. **3.** Data on file. Forest Laboratories, Inc. **4.** Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374:685-694. **5.** US Food and Drug Administration. Atrovent approval history (NDA 019085, 1986). Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed October 19, 2011.

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

Effective with LABAs or short-acting anticholinergics

In the same studies:

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

CONSISTENT EFFECT WITH A CONCOMITANT BRONCHODILATOR[1,3]

DALIRESP with LABAs (Long-acting $ß_2$ Agonists)	✓
DALIRESP with Short-acting Anticholinergics	✓

Study design: A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs and short-acting anticholinergics were allowed and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV_1) were co-primary endpoints. Each study met both co-primary endpoints.

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.

Adverse Reactions

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

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

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

Daliresp® (roflumilast) tablets 500 mcg

 84-12000308T 11/11

DALIRESP™ (roflumilast) tablets **Rx Only**
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

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

Limitations of Use

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

CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events including Suicidality

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

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

Weight Decrease

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

Drug Interactions

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

ADVERSE REACTIONS

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

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

Adverse Reactions in Clinical Studies

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

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

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

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

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

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

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

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

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

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting

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

Musculoskeletal and connective tissue disorders - muscle spasms

Nervous system disorders - tremor

Psychiatric disorders - anxiety, depression

DRUG INTERACTIONS

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

Drugs That Induce Cytochrome P450 (CYP) Enzymes

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

Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

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

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

Human Experience

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

Management of Overdose

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

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

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

Rev 2/2011

84-1020598-BS-T-RMC17137-FEB11

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

PRESIDENT'S REPORT

CHEST Annual Meeting: Past, Present, and Future

Introduction

One of the biggest events for a professional society throughout the year is its annual meeting. ACCP's annual meeting—CHEST—encompasses advances in clinical knowledge and medical innovation in an easily assimilable manner. If this information is appropriately packaged and delivered to the attendees, medical innovation could be linked to positive outcomes measured as process and quality improvement, improved productivity, and better utilization of resources and technology. Such a conference acts as a common platform to share ideas with professional colleagues and mentor future leaders, identifying new research projects in pulmonary, critical care, and sleep medicine. It is about encouraging and inspiring physicians-in-training to learn more about their profession and the icons who have made it what it is today. It is about sharing stories and experiences of those remarkable individuals and medical institutions demonstrating excellence by implementing a technology, process, or other initiatives that have had a positive impact upon patient care outcomes. It is about understanding the nuances of the changing health-care system, with emphasis on quality and value-based purchasing that drives some participants to attend CHEST and learn about the business of medicine. Whatever the reasons, the annual meeting provides fertile grounds for the dissemination of medical information to a closely knit community.

SUHAIL RAOOF, MBBS, FCCP

History

It is fascinating to read about the history of the ACCP annual meetings to realize how teaching formats and techniques utilized today took root over 50 years ago in prior CHEST meetings. The first annual international scientific assembly of the Federation of American Sanatoria (precursor of ACCP) was held in 1935 in Albuquerque, New Mexico. The scientific content, intertwined with business and committee meetings, took 1 day to complete. There were 39 registrants, who had each paid annual membership dues of $5 that gave them access to this meeting. Over the next 10 years, from 1940-1950, the College headquarters moved to Chicago, chapters were formed, fellowships (FCCP) were presented during solemn ceremonies conducted at annual meetings, poster exhibits were launched, and postgraduate courses, predicated on a structured curriculum, were offered. All of these advancements modified the flavor of the ACCP annual meeting. The theme of the meetings branched out from TB to eradication of rheumatic fever, the wonder drug-penicillin, and public health issues. The advent of television permitted a global outreach. A new feature added in this era was the roundtable luncheon, called the "Information Please—in Medicine." The format was interactive, allowing the audience to ask experts questions. This was the precursor to the current day "panel discussions." Of note, annual meetings were cancelled only twice since their inception, in 1943 and 1945, at the request of the Office of Defense Transportation, because of the war. The 1950s postwar tranquility in the United States was punctuated by the Civil Rights Movement and by the incarnation of Elvis Presley's, Chuck Berry's, and Jerry Lee Lewis' rock and roll culture. The parallel explosion to these social events in the pulmonary community was the development of two anti-TB drugs and the discovery of Jonas Salk's polio vaccine. A landmark annual meeting of the College was held in 1950 in Rome. The annual scientific meeting truly became an international forum in which eminent and distinguished scientists, physicians, and world-renowned personalities, such as Alexander Fleming (Nobel Prize recipient), and Richard Overhold (pioneering thoracic surgeon), and Pope Pius XII, came and spoke to the participants. International membership surged with this meeting, with over 50 countries represented. In 1952, the College became cognizant of two other important goals that needed to be accomplished. One was the realization that smoking posed a growing threat to doctors and patients. And the second was the need to harness "motion pictures" as a social media for global education and training. To fulfill the growing needs of the participants to learn about or brush up on pulmonary or cardiology topics, postgraduate seminars were initiated. At their initiation, a fee of $7.50 for the entire day was charged. Postgraduate courses are still delivered presently at the start of each annual meeting.

The importance of chest imaging in diagnosing chest diseases was recognized early in the history of the College. For many years, a single chest radiograph conference was conducted, and an enthusiastic panel split hairs over interpretation of chest radiographs. The concept of a clinical-radiographic-pathology conference was enunciated in 1954 and was determined to be a very instructive and captivating way to teach clinical pulmonary medicine. In 1955, the concept of small group discussions was born, as luncheon panels and evening fireside conferences were conceived and offered. The informal small focus groups were interactive, allowing all present to partake in the discussion. These focus groups paved the way for hands-on workshops and simulation training that are now an integral part of the annual CHEST meetings. In the first 25 years of the annual meeting's inception, New York and New Jersey were the venues for the meeting 10 times. In the 1960s, the College energized its stance on the "no smoking campaign" and established awards and memorial lectures at the meeting. The 1970s saw the change in the name of the journal from *Diseases of the Chest* to *Chest*. With the name change, the scope of the topics in the *Chest* journal and at the annual meeting was significantly expanded to include cardiopulmonary disorders. In 1972, the College limited smoking at its annual meeting to specially designated areas, attracting national attention and public media. At the same time, the committee on Smoking and Health enunciated the Nonsmoking Pledge, which was then administered to initiates (new FCCPs) during the annual meeting. The next decade saw the transitioning of videos to new information delivery and dissemination systems. Personal computers and CD-ROMs slowly started getting popular. It became easier to disseminate enduring education products in a global fashion, providing the impetus for the concept of the "college without walls." Successful heart-lung transplant created excitement and influenced the agenda of the annual meetings. However, this was overshadowed by the AIDS epidemic with its concomitant pulmonary complications, including resurgence of TB and respiratory failure, which consumed the chest medicine community. The 1990s saw advancement of home computers with the creation of online courses. Slowly, a team approach to education and patient care was evolving, which influenced the content of the ACCP annual meetings. To rebrand the annual meeting, and to make the obvious connection with the ACCP intuitively obvious, the annual international scientific assembly was simply abbreviated to be CHEST, and this designation for the meeting remains today.

The membership had expanded to almost 15,000, with just under 100 countries represented. The "college without walls" was truly taking shape. The last 10 years have witnessed a myriad of changes with strengthening of the philanthropic arm of the College—The CHEST Foundation, and utilization of important and sound educational principles to impart focused and highly relevant chest education that is close to the day-to-day practice of private physicians. Literature reviews, case-based learning modules, interesting case discussions packaged as clinical case puzzlers, pro and con debates, and postgraduate seminars gained popularity as effective teaching tools at CHEST. Then dawned the era of simulation education! It was incorporated into the armamentarium of the teaching tools of the ACCP to provide greater hands-on educational experiences, especially to teach new technical skills. This effective method of teaching was promptly trialed at CHEST in 2005 and became an instant success. And finally, in 2007, in an effort to develop a structured curriculum at CHEST, Ed Dellert, the ACCP Education Vice President at the time, proposed that teaching formats utilized to deliver educational offerings at CHEST be delegated into six learning categories:

- Learning Category I–Lecture-Based
- Learning Category II–Self-Directed
- Learning Category III–Evidence-Based
- Learning Category IV–Case- and Problem-Based
- Learning Category V–Simulation
- Learning Category VI–Quality Improvement

Over its 75 years of existence, the ACCP has strived to achieve its distinction as a global leader in clinical education. By utilizing a painstaking process of trial and error and participant feedback to select those teaching techniques that work and are effective, its educational offerings and enduring products are sought nationally and internationally.

CHEST 2011-Hawaii

The annual meeting in Hawaii originally evoked mixed reactions. Would participants be dissuaded by the distance and expense? Would people come alone or with their families? Since this is officially labeled as a holiday resort, would a larger percentage of people register for the meeting and not attend the sessions? Should the College be scaling back on its afternoon and evening educational agenda due to the markedly different time zone and need for family time? As a result of this "resort status," would pharmaceutical companies decline to support many of the international attendees?

CHEST 2011 proved to be an eminently successful meeting under the guidance of Dr. David Gutterman, ACCP President; and Dr. Kevin Chan, Chair of Scientific Program Committee. There was a total of 6,321 attendees (registrants), with almost 525 guests. International participants constituted nearly 33% of the professional attendees. This was the second highest attendance ever

Continued on following page

Continued from previous page

recorded in CHEST history and the highest international attendance on record. The total number of educational sessions organized was approximately 340. Nearly 560 attendees participated in simulation stations.

At the time this article was being written, the composite evaluation of the attendees was not available. However, the Board of Regents was polled on December 5, 2011. Their responses (N=14) are summarized below.

How did Hawaii compare with nonresort locations for the CHEST annual meeting?
71% felt it was a better location for the annual meeting and served as a "fantastic venue," which allowed participants to combine the conference with a family vacation. There was a plethora of activities in which to partake. Several people appreciated the casual dress code, which made it a more relaxing experience. And everyone loved the weather. The remaining respondents were either neutral or felt that the variety of activities that individuals had to chose from was distracting to the scientific sessions. A few people commented on the time and expense of travel to Hawaii.

Top five aspects of CHEST 2011 that you liked the most.
The board felt that greater participation of international colleagues was a welcome change. Many appreciated the wide spectrum of formats utilized for delivering educational content, including simulation training, small focus groups, interactive sessions, debates, and literature reviews, coupled with the diversity of topics. Others commented on the excellent fellows' courses. Some board members liked the new concept of "Centers of excellence," outreach to the local medical community, and the integration of asthma and COPD coalition activities. A shorter convocation ceremony and the OneBreath luau also featured prominently in the "good innovations" category. Finally, participants appreciated the reliable and frequent bus shuttle service.

Top five things you would like to see changed at the CHEST annual meeting.
Many people felt that the convocation ceremony and opening sessions, including keynote speaker session, were poorly attended. The size of the rooms was inappropriate for some of the presentations, and poster moderating was difficult due to several authors not being present at their posters. Two board members remarked that leadership training sessions were conspicuous by their absence. Others commented on the need for more emphasis on health-care reform and "wave change trends" in health care. The board encouraged the expanded use of technology to set up the "app" to coordinate activities for individual attendees and to navigate between different sessions quickly. Wi-Fi access featured prominently in the "must provide list" for the participants. Some commented on the need for more time for networking, meetings, and direct interaction with general membership, possibly in a town hall format.

THE CHEST MEETING SHOULD BE YOUR ADVANCED CLINICAL EDUCATION HOME AND INNOVATION HUB.

CHEST 2012-Atlanta

"Continual improvement is an unending journey." *–Lloyd Dobyns and Clare-Crawford-Mason*
Based upon the experiences gained, here is what Dr. Doreen J. Addrizzo-Harris, FCCP, Chair of Scientific Program Committee 2012 had to say:

CHEST 2012 Atlanta is planned to be a very exciting and innovative meeting. In addition to the core pulmonary, critical care, and sleep sessions, there will be greater focus in several areas:

- Our global focus will continue with a dedicated session each day on global issues led by leaders in our international community.
- There will be special sessions on chest infections, which will be partnered with members from the CDC in Atlanta.
- We will highlight radiology topics, with a special track linking to key pulmonary and critical care topics.
- We will also be increasing our practice-based learning sessions that have been very popular small group learning sessions led by key faculty.
- CHEST 2012 will offer a 2-day "for the pulmonary practitioner" track so that those who cannot spend the full week away from work will be able to get a quick update highlight in eight key areas.
- A special focus on the area of leadership development and mentorship, with several symposia, is planned to enhance learning in these areas.
- There will be every effort to make sessions interactive and multi-disciplinary whenever feasible.

Improving the scientific content of CHEST is half the story. Paul Markowski, EVP-CEO, Ed Dellert, and the ACCP staff are working diligently to enhance the planning and layout of the meeting. Some of their general recommendations, which we will try to implement, are the following:

- Have a separate opening ceremony for global education day, possibly with an international keynote speaker
- Daily opening sessions will emphasize College themes that affect College members. This year, we will strive to bring our members together at daily opening sessions to discuss areas of great importance to our profession.
- Restructuring the Convocation and named awards ceremony.
- Branding of pulmonary diseases through, the OneBreath® Campaign.
- Identifying and recognizing Centers of Excellence that represent hospitals, private practices, pharmaceutical companies, and businesses.
- Reaching out to the medical and public community of Atlanta, sharing information about the ACCP, The CHEST Foundation's OneBreath Campaign, and our clinical content experts. Throughout the week of October 20-25, 2012, the ACCP and The Foundation plan to provide world-renowned speakers from CHEST 2012 to local medical institutions in Atlanta. The CHEST Foundation will reach out to the public community and selected public school districts to educate children about the effects of tobacco, secondhand smoke, and managing asthma.

Medical innovation at CHEST 2012 is about the value and importance of experimentation. Building CHEST 2012 is a complicated process and involves subtle interdependencies along a pathway that has many variables. It takes its roots from a dynamic system of bringing together great ideas, advanced clinical education, research, and the unique networking opportunities that it presents. The CHEST meeting should be your advanced clinical education home and innovation hub. It is a meeting where the mastering of the variables and experimentation allow us together to create new educational products, pathways for learning, and services that achieve what we hope will accelerate and have a positive and lasting impact on the patients we care for and serve.

Join me and your colleagues for a truly innovative experience at CHEST 2012, Atlanta, Georgia, October 20-25, 2012. ■

Accreditation With Commendation for the ACCP

The Accreditation Council for Continuing Medical Education (ACCME) has awarded the ACCP Accreditation With Commendation for a 6-year term, the maximum accreditation granted any organization.

This distinction places the ACCP in the highest tier of all CME providers, which includes some of the nation's most prestigious medical schools and professional medical societies. ACCME-accredited providers certify educational activities for *AMA PRA* (American Medical Association's Physician's Recognition Award) *Category 1 Credit*™, which is used by state licensing boards and boards of medical specialties to relicense and recertify physicians in their areas of specialty.

ACCME accreditation is a tool to ensure the medical community and the public that such activities provide physicians and other health-care providers with interventions that improve the practice and delivery of the best standards of care. The decision for this accreditation was based on the review of the ACCP's self-study report, evidence of performance-in-practice, and an accreditation interview. In achieving accreditation with commendation, the ACCP demonstrated:

- Integration of CME into the process for improving practice
- Utilization of noneducational strategies to enhance change
- Identification of factors outside its control that impact patient outcomes
- Implementation of educational strategies to remove, overcome, or address barriers to change
- Collaboration and cooperation with multiple stakeholders
- Participation within an institutional framework for quality improvement
- Position to influence the scope and content of its educational interventions.

The ACCP implemented several initiatives in line with the ACCME criteria for commendation, including the Critical Care Ultrasound Certificate of Completion program, the Venous Thromboembolism Performance Improvement Module, The CHEST Foundation's OneBreath® Campaign, the Tobacco Dependence Toolkit, advocacy and interventions addressing the critical care workforce shortage, and participation in quality improvement efforts of the National Quality Forum, The Physician Consortium for PI, CMS, and the AHRQ.

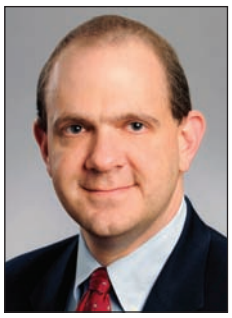
This recognition demonstrates the collaboration of volunteer leaders on the Education Committee and others, including the Health and Science Policy Committee, Quality Improvement Committee, Practice Management Committee, and The CHEST Foundation, along with a cross-section of staff, who provide a program that excels at the design and implementation of the highest caliber of medical education.

This distinctive accreditation is a tribute to the leadership role the ACCP plays in the quality of health-care education it provides to its members and others throughout the pulmonary, critical care, and sleep medicine communities. ■

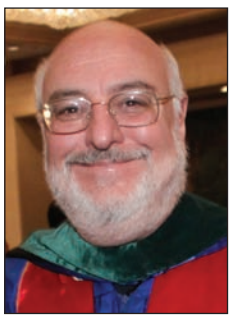
New Editors and Editorial Advisory Board Members

New Section Editors for Sleep Strategies and Critical Care Commentary

Dr. David Schulman, FCCP, is an Assistant Professor of Medicine at Emory University School of Medicine; he also serves as Associate Division Director for Education for Pulmonary, Allergy and Critical Care Medicine and Director of the Pulmonary and Critical Care Medicine Fellowship Training Program. Dr. Schulman serves the College as Vice-Chair of the ACCP Sleep NetWork and a member of the CHEST Scientific Program Committee. His interests are in the management of mild sleep-disordered breathing and education about sleep disorders.


DAVID SCHULMAN, MD, FCCP

Dr. Peter Spiro, FCCP, is a Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, and Head of the Medical ICU, Division of Pulmonary Medicine, Harlem Hospital, in New York. He has served as Chair of the ACCP Council of NetWorks and Chair of the Critical Care NetWork. He was the 2011 recipient of the Roger C. Bone Advances in End-of-Life Care Award. Dr. Spiro's special interests include outcomes and quality, delivery models and access, and palliative end of life care.


PETER SPIRO, MD, FCCP

New *CHEST Physician* Editorial Advisory Board Members

Dr. W. Michael Alberts, FCCP, is the new Medical Editor in Chief of *CHEST Physician*. He is a Past President of the ACCP and currently the Treasurer of The CHEST Foundation. He is Professor of Oncology and Medicine in the Department of Interdisciplinary Oncology at the University of South Florida College of Medicine in Tampa, FL, and Chief Medical Officer at the H. Lee Moffitt Cancer Center and Research Institute. He serves as a *CHEST* Editorial Board Member and has served the College in many ACCP leadership roles, including chairing the Education Committee and the Council of Governors and serving on the Board of Regents and Executive Committee of the Board. His research and scholarly interests include the diagnosis and management of lung cancer, occupational airways disorders, and the business of medicine.


W. MICHAEL ALBERTS, MD, FCCP

Dr. Paul Selecky, FCCP, is the immediate past Editor in Chief of *CHEST Physician*. He is Clinical Professor of Medicine, UCLA; and Medical Director of the Pulmonary Department, Sleep Disorders Center, and Palliative Medicine Service, Hoag Hospital, Newport Beach, California. He is a past chair of the ACCP Education Committee and a past president of NAMDRC. ACCP committee participation includes Ethics, Government Relations, and Health and Science Policy, and he is a past chair of the Respiratory Care NetWork. His special interests are in sleep medicine and end-of-life care.


PAUL SELECKY, MD, FCCP

Dr. Lary A. Robinson, FCCP is a Senior Member, Moffitt Medical Group and a practicing thoracic surgical oncologist in the Division of Thoracic Oncology, Moffitt Cancer Center, Tampa, Florida. He is the past member of the ACCP Critical Care Network, the ACCP Steering Committee for the Lung Cancer Initiative, and Section Editor of the 1st and 2nd editions of the ACCP Lung Cancer Guidelines. He is a current member of the ACCP Ethics Committee. Dr. Robinson's interests encompass all aspects of thoracic surgery and thoracic oncology.


LARY A. ROBINSON, MD, FCCP

Dr. Steven Q. Simpson, FCCP, is Professor, The University of Kansas School of Medicine, Division of Pulmonary and Critical Care Medicine, in Kansas City, Kansas. He is the Third Eli Lilly and Company Distinguished Scholar in Critical Care Medicine and currently is Chair of the Critical Care NetWork. He has served the College in several positions, including ACCP Governor and member of the CHEST Scientific Program Committee. Dr. Simpson's interests are in sepsis diagnosis and treatment and all areas of critical care medicine.


STEVEN Q. SIMPSON, MD, FCCP

Dr. Susan Millard, FCCP, is a pediatric pulmonologist at Helen DeVos Children's Hospital (HDVCH) in Grand Rapids, Michigan. She is an Associate Professor of Pediatrics and Human Development at Michigan State University and is the Director of the Pediatric Pulmonary Diagnostics Laboratory at HDVCH and is in charge of clinical research for the division. She also is on the Drug Safety Monitoring Board of the Cystic Fibrosis Foundation. Dr. Millard previously was the Chair of the ACCP Pediatric Chest NetWork and has served on the Marketing Committee. Her special interests are cystic fibrosis clinical research, home mechanical ventilation, and bronchopulmonary dysplasia.


SUSAN MILLARD, MD, FCCP

Dr. Vera A. De Palo, FCCP, is Associate Chief of Medicine at Memorial Hospital of Rhode Island and a member of the RI Healthcare Reform Commission. She has served the ACCP as Governor for Rhode Island; Chair of the Council of Governors; member of the Board of Regents and on the Executive Committee; member of ACCP Government Relations, Credentials, and Membership Committees, and Chair of the Membership Committee. CHEST Foundation service has included being a trustee and a member of its Pro Bono and Humanitarian Awards Review Committees. Dr. De Palo's interests are in asthma/COPD, critical care, end-of-life, quality and safety, pulmonary infections, ventilator-associated pneumonia, and central line-associated infection. She now serves as Deputy Editor for *CHEST Physician*. ■


VERA A. DE PALO, MD, FCCP

Many Faces of CHEST 2011 in Honolulu

First-ever International Opening Session played host to China dignitaries who informed us of health-care issues in China. Pictured is Renli Qiao, MD, FCCP, who chaired the meeting with Chunxue Bai, MD, FCCP.

The 2011 keynote speaker, Sherwin Nuland, MD, packed the house.

The OneBreath® luau, with entertainers and artisans, gave us a taste of Hawaiian culture.

Pictures from CHEST 2011 are available for viewing and purchase at www.lagniappestudio.com/chest2011. For more about the annual CHEST meeting, don't miss the President's Report in this issue.

Our new FCCPs standing proudly on the dais.

Simulation education was more popular than ever, drawing over 500 registrants.

PHOTOS COURTESY ACCP

Congratulations to the Many Winners at CHEST 2011

ACCP Honor Awards

▶ *Alfred Soffer Award for Editorial Excellence*
Michael B. Zack, MD, FCCP
▶ *Alton Ochsner Award Relating Smoking and Disease*
Shabih U. Hasan, MBBS
▶ *Master FCCPs*
Robert G. Johnson, MD, Master FCCP
Paul A. Kvale, MD, Master FCCP

The CHEST Foundation Awards

In 2011, The CHEST Foundation offered more than $500,000 in awards to support research and volunteer work related to pulmonary, critical care, and sleep medicine.
▶ *Third GlaxoSmithKline Distinguished Scholar in Thrombosis*
James D. Douketis, MD, FCCP
▶ *D. Robert McCaffree, MD, Master FCCP, Humanitarian Awards*
$15,000 Award
Thomas R. Gildea, MD, FCCP
Thomas Lahiri, MD, FCCP
$10,000 Ambassadors Group Award
Peter Karczmar, MD, FCCP
$5,000 Award
Raghu R. Sundaram, MBBS
▶ *Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency*
Andrew John Sandford, PhD
▶ *Roger C. Bone Advances in End-of-Life Care Award*
Peter Spiro, MD, FCCP
▶ *The CHEST Foundation California Chapter Clinical Research/Medical Education Award*
Sharon J. De Cruz, MD
▶ *The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women's Lung Health*
Danit Ariel, MD
▶ *OneBreath™ Clinical Research Award in Lung Cancer*
Saikrishna S. Yendamuri, MD, FCCP

Alfred Soffer Research Award Winners

$1,500 Award Winners
Kristin Fraser, MD
H. Nicole Tran, MD
$1,000 Award Winners
Sajid Haque, MD
Dixie Harris, MD
Randall Keyser, PhD
Vickie Shannon, MD

Canadian Thoracic Society Awards

▶ *CTS Annual Christie Memorial Lecture*
Malcolm R. Sears, MBChB
▶ *CTS Institute of Circulatory and Respiratory Health Distinguished Lecture in the Respiratory Sciences*
Qutayba Hamid, MD, PhD

Young Investigator Award Winners

$2,000 Award Winners
Tomas Konecny, MD
Michele Kong, MD
$1,250 Award Winners
Jonathan Caronia, DO
Matthew Rondina, MD
Sophia Williams, MD, MPH

Top Five Poster Award Winners

Muhammad Akbar, MD
Jared Chiarchiaro, MD
Masafumi Matsui, MD
Alexandra Quittner
Norihisa Shigemura, MD

Case Report Awards

Mohammad Syed, MD, MBBS
Satish Chandrashekran, MD
Amanda Godfrey, MD
Richard Patch, MD
Amir Emtiazjoo, MD, MSc
Annie Harrington, MD
Rabih Halabi, Md
Sean Roark, MD
Darlene Nelson, MD
Naveed Hasan, MBBS
Allison Cihla, MD
Jimmy Suvantne, MD
Angel Coz Yataco, MD
Choo Khoon Ong, MD
Matthew Aboudara, MD
Michael Lanspa, MD
Adam Wellikoff, MD
Melhem Imad, MD
Gregory Wiaterek, MD
Tathagat Narula, MD, MBBS
Christine Gould, MD
Rahat Hussain, MD
Maher Ghamloush, MD
Minggen Kuo, MD
Tathagat Narula, MD, MBBS
Venkata Dodda, MBBS
Mauricio Danckers Degregori, MD

CHEST Challenge Winners

▶ *First Place: National Capital Consortium*
LT Gregory S. Fuhrer, MC, USN
CPT Jordanna Hostler, MC, USA
LT Andrew I. Philip, MC, USN
▶ *Second Place: University of Missouri - Pulmonary & Critical Care Medicine*
Tareq M. Abu Salah, MBBS
Jason Goodin, DO
Casey L. Stahlheber, MD
▶ *Third Place: UCSF Fresno Department of Pulmonary and Critical Care*
Garrett R. Bird, MD
LCDR David L. Collins, MC, USN
Chitra Kandaswamy, MBBS

CHEST 2011 Bingo Winners

▶ *CHEST Bingo (Monday Winners)*
Teresa Lentz, RN – Camden, Delaware
Robert S. Wang, MD – Schenectady, New York
Jordanna Hostler, MD – Bethesda, Maryland
Arthur C. Crisostomo, MD, FCCP – Waukesha, Wisconsin
Winston Liao, PhD – Raleigh, North Carolina
▶ *COPD Bingo (Tuesday Winners)*
Robert I. Goodman, MD – Los Angeles, California
Michelle Hackshaw, PhD – West Point, Pennsylvania
Ali Jabari, MD – Dedham, Massachusetts
Kenneth W. Landis, MD, FCCP – Inglewood, California
Lilibeth A. Pineda, MD, DPM, FCCP – Phoenix, Arizona
▶ *PAH Bingo (Wednesday Winners)*
Juantina Johnson, MD, FCCP – New Orleans, Louisiana
Suganda Phalakornkul, MD – Elmhurst, New York
Franklin J. Myers, III, MD, FCCP – Mechanicsburg, Pennsylvania
Luis E. Chug, MD – Mission, Kansas
Armand M. Ryden, MD – Los Angeles, California

OneBreath® iPad2 Winner

Rajat Kapoor, MD

Winners of the OneBreath 5K Walk/Run can be viewed at http://pseresults.com/events/415/results.

The CHEST Foundation Awards Program for 2012

The tradition of supporting research and volunteer work will continue in 2012. Watch for the application site to open in January at OneBreath.org. ■

OneBreath® Apple iPad2® Winner

Dr. Rajat Kapoor from Troy, Michigan, was the winner of The CHEST Foundation's OneBreath iPad2 drawing, held during CHEST 2011. Everyone who signed up to become a member of OneBreath® during CHEST 2011 was entered into the drawing.

Dr. Kapoor is a fellow in Pulmonary and Critical Care at Wayne State University in Detroit, Michigan. He has been a member of the ACCP for almost 2 years and attended CHEST for the first time in 2011. When asked which part of the CHEST meeting stood out the most, he replied, "the radiology lectures and case puzzlers."

Dr. Kapoor has found the OneBreath Web site, (www.onebreath.org) to be a great source for information and has referred many of his patients to the Quit Smoking area of the site.

Lung and heart health impacts everyone, everyday, and The CHEST Foundation's OneBreath campaign inspires people to take care of their lungs and heart and to never take their next breath for granted. Join OneBreath at OneBreath.org, and become a part of this global community that is focused on lung and heart health. ■

SLEEP STRATEGIES

Sleep in Women: A Changing Perspective

As with many other specialties, sleep medicine has been shifting toward helping clinicians obtain a better understanding of gender-specific issues in disorders and disturbances. It is easier today to appreciate the complex dynamics of biological, psychosocial, and cultural factors that define sleep patterns and problems in women. Sleep in women changes across their life spans, with three major shifts likely due to hormonal differences: at the onset of the menstrual cycle, during pregnancy, and during the perimenopausal period.

The National Sleep Foundation's 2007 Sleep in America Poll revealed that 46% of a sample of women aged 18 to 64 years in households across the continental United States had sleep problems almost every night, with only 39% reporting sleeping well most nights or every night. Nearly 3 in 10 women reported a good night's sleep only a few nights a month or less. The most common complaint, difficulty falling asleep or waking too early with an inability to return to sleep, occurred in more than one-third of those surveyed at least a few nights a week. According to the Sleep Heart Health Study, women are significantly more likely to report difficulty initiating and maintaining sleep than men (42.4% vs 32.5%), whereas men are twice as likely to have sleep-disordered breathing (Baldwin et al. *Sleep.* 2001;24[1]:96).

Insomnia occurs almost twice as often in women compared with men; women also have a significant increase in sleep-onset latency and a significant decrease in sleep efficiency and sleep quality, most often during the luteal phase of the menstrual cycle (Soares. *Arch Womens Ment Health.* 2005;8[4]:205). These symptoms are also pronounced during the onset of menses in those who experience premenstrual syndrome and are of increased severity in those with premenstrual dysphoric disorder, with greater luteal increases in daytime sleepiness likely due to lower progesterone levels (Manber and Bootzin. *Health Psychol.* 1997;16[3]:209).

More data exist on female sleep during pregnancy than during any other phase of the female life cycle. The vast majority of women who were pregnant or in the postpartum period (84%) in the 2007 Sleep in America Poll reported sleep problems at least a few nights a week. During pregnancy, sleep is affected by both hormonal changes and physical discomfort. Significant changes in sleep patterns are evident by 11 to 12 weeks of gestation, with a notable increase in total sleep time but less deep sleep and more nocturnal awakenings. Pregnancy-induced changes in the physiology and anatomy of the upper airway make women more prone to snoring, paving the way for the development of obstructive sleep apnea and nocturnal desaturation, which may be particularly severe during the third trimester when oxygen stores in the lung are already reduced due to lung compression from the enlarging uterus. Pregnant women who snore are at increased risk for preeclampsia, pregnancy-induced hypertension, and fetal growth retardation, even after adjustment for weight, age, and tobacco use (Franklin et al. *Chest.* 2000;117[1]:137). This has important implications for the unborn child as well because severe sleep deprivation during the pregnancy period is associated with increased sleep disturbance for the offspring during childhood (Armstrong et al. *J Paediatr Child Health.* 1998;34[3]:263). Sleep impairment is not limited to the period of pregnancy; sleep disturbance is even more severe during the first postpartum month, an effect that is most pronounced in first-time mothers (Lee et al. *Obstet Gynecol.* 2000;95[1]:14).

Up to one-half of women complain of sleep problems during the menopausal transition, some of which can be attributed to hot flashes and night sweats. Short-term hormone replacement therapy, antidepressants, and nonpharmacologic therapy have been shown to have a beneficial effect on sleep quality during this time. Studies have also shown that the delicate interplay of hormones during the reproductive years influences sleep architecture, with progesterone increasing the latency to REM sleep and decreasing the overall percentage of REM sleep, and estrogen possibly doing the opposite (Manber et al. *Sleep.* 1999;22[5]:540). The Study of Women's Health Across the Nation (SWAN) demonstrated that an adjusted odds ratio of reported trouble sleeping was 29% higher in perimenopausal women compared with those who were premenopausal. Different hormones predicted trouble sleeping in the two groups, with low follicle-stimulating hormone levels associated with increased trouble sleeping in premenopausal women. Levels of pregnanediol glucuronide, a progesterone metabolite, was a better marker for predicting trouble sleeping during the peri-menopausal period (Kravitz et al. *Arch Intern Med.* 2005;165[20]:2370).

While work-related sleep restriction has classically affected men, times are changing. Eighty percent of working women report fatigue, and 60% has difficulty sleeping. Shift-working women, like their male counterparts, are prone to altered sleep and circadian rhythms and also report higher rates of sleeping pill, tranquilizer, and alcohol use (Gordon et al. *Am J Public Health.* 1986;76[10]:1225). Women are physiologically less capable of metabolizing similar amounts of alcohol compared with men (Frezza et al. *N Engl J Med.* 1990;322[2]:95); whether this translates into an increased risk for alcohol-induced sleep disturbances is unknown at this time.

It is not all bad news for the fairer sex, though. Women have a longer total sleep time albeit a longer sleep latency, less stage 2 sleep, and more slow-wave sleep than age-matched men (Ohayon et al. *Sleep.* 2004;27[7]:1255). Also, women with sleep-disordered breathing do not have an increased risk of motor vehicle accidents when compared with their well-rested female counterparts, even when controlled for age, alcohol use, and miles driven. This is in stark contrast with men who snore and those with an apnea-hypopnea index >5/h, who are at three times the risk of a motor vehicle accident compared with similar healthy control subjects (Young et al. *Sleep.* 1997;20[8]:608). It is unknown whether this is due to a predominantly male instinct to ignore potentially dangerous sleepiness and get behind the wheel or an actual difference between the sexes in resistance to impairment of concentration and motor skills consequent to sleep-disordered breathing.

Given that we are now more cognizant of the differences in sleep physiology and architecture between the sexes, and indeed within the life cycle of women, the onus is on present and future researchers in sleep medicine to study large samples of women to better identify clinically relevant causes and outcomes of sleep disruption. ■

Dr. Misha Peter
Fellow, Division of Pulmonary and Critical Care

Dr. Ritu Grewal, FCCP
Assistant Professor of Medicine
Attending Physician, Sleep Disorders Center
Attending Physician, Division of Pulmonary Medicine
Thomas Jefferson University Hospitals
Philadelphia, PA

In Remembrance

Brian J. Whipp, PhD, DSc, died on October 20, 2011, at the University of Wales Hospital in Cardiff, Wales, United Kingdom.

BRIAN J. WHIPP, PHD, DSC

Dr. Whipp received his PhD in physiology from Stanford University, and he then set out on what was to become an illustrious career in physiology, both as a research investigator and a teacher. He taught at the Harbor-UCLA Medical Center in Torrance, California, proceeding through the academic ranks to become Professor of Physiology and Medicine and Vice-Chairman of UCLA's Department of Physiology. During this period, he was awarded an Established Investigatorship of the American Heart Association and was a Visiting Research Scientist at Oxford University. In 1992, he returned to the United Kingdom to become Professor and Chairman of the Physiology Department at the University of London's St. George's Hospital Medical School.

Dr. Whipp was a recipient of the ACCP Distinguished Scientist Honor Lecture Award in 2007.

Dr. Whipp was a well-respected and recognized researcher with interests centered on the control of ventilation and pulmonary gas exchange during exercise in health and disease, with special reference to the nonsteady state. In addition to more than 300 publications on these topics, he was author or coauthor of nine books and monographs. He was also an accomplished teacher, combining scientific rigor with humor, wit, and enthusiasm.

Dr. Whipp retired from the University of London's St. George's Hospital Medical School in 2001. He remained active since that time, working from his home in the Welsh village of Crickhowell and presenting many invited lectures worldwide. ■

Lessons for January

PCCSU
PULMONARY, CRITICAL CARE, SLEEP UPDATE

- **Nonspecific Interstitial Pneumonia: A Review Article.** *By Dr. Mary E. Strek, FCCP; and Dr. Imre Noth, FCCP*
- **Inhaled Nitric Oxide: Therapeutic Uses and Potential Hazards.** *By Ivan Katz, RRT*
- **Imaging and Differential Diagnosis of Cystic Lung Disease.** *By Dr. Isabel B. Oliva; Dr. Danielle Antin-Ozerkis; and Dr. Ami N. Rubinowitz*

2011 Centers of Excellence Enjoyed by Attendees

On October 23, 2011, the American College of Chest Physicians opened its doors to present a new concept that enabled CHEST 2011 attendees to interact with colleagues and industry in a venue that showcased innovative ideas and best practices by a medical university, hospitals, clinics, and military medical teams. The 10 Centers of Excellence (COE) and 3 industry-supported TouchDown Stations (TDS) were visited by 500 to 600 people.

Evaluations indicated attendees enjoyed and learned from the presentations and were able to take ideas home with them for implementation in their own practices. Comments from some of the presenters and attendees follow.

"The Centers of Excellence was an uncrowded, unhurried oasis and a chance to see cutting-edge clinical and educational initiatives and to really TALK to their developers." – *Barbara A. Phillips, MD, MSPH, FCCP*

"The ACCP Centers of Excellence showcased the very best in chest medicine. Selected on the basis of excellence and effectiveness, the participants were provided an ideal opportunity to share their successes with CHEST 2011 attendees. The relaxed and comfortable atmosphere allowed programs to gamer feedback and advice regarding how to make them even more effective and an opportunity for CHEST 2011 attendees to speak directly with the engineers of each distinguished program. The ACCP Centers of Excellence was truly a platform of best practices from around the country on exhibition for those who attended CHEST 2011. With the positive excitement generated this year, I know the Centers of Excellence at CHEST 2012 in Atlanta, Georgia, will be even bigger and better." – *Darcy D. Marciniuk, MD, FCCP*

"Our not-for-profit, Not One More Life, Inc (NOML) (www.notonemorelife.org), was honored to be selected as a Center of Excellence at CHEST 2011. This inaugural Centers of Excellence event allowed Not One More Life and other activities an unprecedented level of exposure among our colleagues at the ACCP's annual meeting. This exposure and the generous award associated with our selection supports the continued growth and expansion of our mission. This mission is to address disparities in morbidity and mortality attributable to asthma and other lung diseases in high risk populations. This is accomplished by free programs of patient and provider education, screening, referral, and follow-up offered in partnership with local communities of faith. Subsequent to CHEST 2012, NOML has received no fewer than 12 requests to expand our model to other cities around the United States, potentially bringing our national network to over 24 communities." - *LeRoy M. Graham, MD, FCCP*

Additional information about the 2011 Centers of Excellence and its updates for CHEST 2012 will appear in subsequent issues of *CHEST Physician*. ■

This Month in *CHEST:* Editor's Picks

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

ORIGINAL RESEARCH

▶ **Race and Sex Differences in Response to Endothelin Receptor Antagonists for Pulmonary Arterial Hypertension.** *By Dr. N. B. Gabler et al.*

▶ **Interpreting Lung Function Data Using 80% Predicted and Fixed Thresholds Identifies Patients at Increased Risk of Mortality.** *By Drs. D. M. Mannino; and E. Diaz-Guzman.*

▶ **The Impact of Tiotropium on Mortality and Exacerbations When Added to Inhaled Corticosteroids and Long-Acting Beta-Agonist Therapy in COPD.** *By Dr. P. M. Short et al.*

SPECIAL FEATURE

▶ **Multisociety Task Force for Critical Care Research: Key Issues and Recommendations.** *By Drs. C.S. Deutschman; T. Ahrens; C. B. Cairns; C. N. Sessler; P. E. Parsons; for the Critical Care Societies Collaborative/USCIITG Task Force on Critical Care Research.*

NETWORKS

Applied Medical Informatics and Other Challenges

Clinical Pulmonary Medicine

The Challenge of Applied Medical Informatics for the Chest Physician

Applied medical informatics (AMI) is an emerging field that is evolving at a rapid pace. While medical informatics encompasses a myriad of disciplines, the basic understanding of AMI for most chest physicians remains "the science of processing information/data for storage and retrieval." Unfortunately, the uptake and implementation of AMI has been mediocre (Blumenthal and Tavenner. *N Engl J Med*. 2010;363[6]:501).Futuristic developments in AMI are exciting as we move toward virtualizing of medical practice, utilizing many diverse technologies, such as remote radiograph interpretation, electronic office visits, and the virtual ICU. The integration of electronic medical records (EMR) into a clinical practice, even the smallest of offices, is the foundation of AMI.

EMR, in practical terms, comprises three major components: (1) a results-reporting information system(RRIS); (2) a computerized physician order-entry system (CPOE); and (3) a clinical decision support system (CDS).CPOE is the most critical component of EMR and leads the way to CDS, guidelines, and care pathways. The barriers to successful implementation of EMR include, but are not limited to, the following: complexity of the EMR, cost of change, time commitment, clinician expectations, interoperability, understanding clinical workflow, and other competing agendas (Bria. *Chest*. 2006;129[2]:446).

Having been at the threshold of launching a new era of AMI-enabled American health care, the failure is disappointing. In order to achieve what was anticipated, we need to be more knowledgeable, demanding, and involved with the introduction of information tools and systems into health care (Shortliffe EH. *Health Aff*. 2005; 24[5]:1222). We need to emphasize greater incorporation of medical knowledge, evidence-based medicine, and clinical decision support. Such advancement will achieve realization of the delivery of cost-effective best care to our patients. Only close collaboration between the multidisciplinary team of clinicians and technical experts can make this happen (Bria. *Chest*. 2006; 129[2]:777). Finally, laying firm timelines for change, with strong directives from the federal, state, local, payer, provider, and user consortia, will help chest physicians reach the lofty goal of full integration of AMI into their profession.

Dr. Satyendra Sharma, FCCP
Steering Committee Member

Cultural Diversity in Medicine

Raising Awareness in a Diverse Population for Better Outcomes

In an era of diversity in health care, the health practices that relate to pregnancy, childrearing, and medically related attitudes of women who identify themselves of Vietnamese origin are not at a level of sensitivity for health-care providers to deliver the best care to this population. Premature, low-birth-weight infants can have serious respiratory consequences. Vietnamese women usually have their children at home along traditional patterns with no medical attendees.

Medical practices are integrally linked to cultural traditions and, thus, health-care providers need to be made aware of the particular beliefs and practices of Asian-Vietnamese woman in order to provide the appropriate level of care that preserves their cultural value and identity and leads to increased survival of both mother and infant.We need awareness, sensitivity, and an understanding of these issues as a precursor to serve this community. The development of a crosscultural competence allows practitioners to feel confident in issues of nonverbal communication (facial expression, eye movement, and body posture), physical spacing, and communication (translation expressions vs actual words) that one can handle a more diverse set of health-care beliefs and behaviors. An individual can maintain his or her cultural identity but must adapt within the larger dominant community. Just as one would want to be sensitive (in a multicultural sense), a program needs to reflect on a leadership style (clinical alternatives to care) and the qualities one needs to focus on in the way we can deal with crisis (acute care emergencies) management and still maintain particular beliefs.

Alan Roth, MS, MBA, RRT
Steering Committee Member

Cardiovascular Medicine and Surgery

Stem Cells in Myocardial Infarction Repair

Mechanism of restoration of cardiac function after stem cell transplantation remains unclear. Apoptosis of transplanted cells seems to modulate local tissue reaction that can repress myocardial apoptosis and lead to improved cardiac outcome. In the BOOST trial (Wollert et al. *Lancet*. 2004;364[9429]:141), intracoronary infusion of bone marrow cells (BMC) into the infarct-related artery resulted in improved left ventricular ejection fraction at 6 months. Selective intracoronary transplantation of autologous, mononuclear BMC positively impacted myocardial regeneration and neovascularization and postinfarction remodelling processes (Strauer et al. *Circulation*. 2002;106[15]:1913). At the present time, it appears that BMC transplantation can lead to (1) metabolic regeneration of infarcted myocardial tissue in humans with an increase in maximum oxygen uptake; (2) improvement in perfusion in the ischemic region; and (3) improvement in exercise capacity in patients with end-stage ischemic cardiomyopathy, improved ejection secondary to a reduction in infarct size, and better recovery of regional systolic function.

Future goals for BMC studies will be to identify therapeutic cell population, determine the efficacy, and prevent atherosclerosis or restenosis in remodelling myocardium after myocardial infarction.

Dr. Roberto Carbone, FCCP,
Steering Committee Member
Dr. Alberto Ballestrero
Dr. Vincenzo Savarino

CPAP Reduced Metabolic Syndrome in OSA Patients

BY MARY ANN MOON
Elsevier Global Medical News

Continuous positive airway pressure therapy improved several components of metabolic syndrome along with obstructive sleep apnea in patients who had both disorders, according to a report in the New England Journal of Medicine.

In most cases, only one component of the metabolic syndrome improved significantly after CPAP, but that improvement was significant enough to "reverse" the syndrome, said Dr. Surendra K. Sharma of All India Institute of Medical Sciences, New Delhi, and his associates.

No particular component stood out as being the most responsive to CPAP; statistically significant improvements were seen in systolic blood pressure (BP), diastolic BP, total cholesterol, non-HDL cholesterol, LDL cholesterol, triglycerides, glycated hemoglobin, body mass index, and visceral and subcutaneous fat. "These results suggest a significant clinical benefit that will lead to a reduction in cardiovascular risk," they noted.

To examine the effect of CPAP on components of metabolic syndrome, the researchers recruited 86 patients aged 30-65 years who had moderate or severe OSA. All the patients reported excessive daytime somnolence. A total of 75 study patients (87%) had metabolic syndrome, and the remainder had some of the components of metabolic syndrome.

These patients were randomly assigned to undergo either CPAP or sham CPAP for 3 months, followed by a washout period of 1 month. They then crossed over to receive the other intervention for 3 months. The sham CPAP was not discernible to the study subjects or the investigators.

Metabolic syndrome resolved in 14 (20%) of the study subjects after CPAP. This was due to decreased BP in five; decreased fasting blood glucose in two; decreased triglycerides in two; increased HDL cholesterol in three; improved triglycerides plus HDL cholesterol in one; and improved triglycerides, HDL cholesterol, and fasting blood glucose in one, Dr. Sharma and his colleagues said. Symptoms of the syndrome developed in three patients who did not have metabolic syndrome at the start of the study.

Overall, CPAP was associated with a mean decrease in systolic BP of 3.9 mm Hg, a mean decrease in diastolic BP of 2.5 mm Hg, a mean decrease in total cholesterol of 13.3 mg/dL, and a mean decrease in triglycerides of 18.7 mg/dL.

CT scans revealed a significant decrease in both visceral and subcutaneous fat, which was accompanied by a decrease in BMI. "These findings could be secondary to a decrease in daytime somnolence and a consequent increase in physical activity" (N. Engl. J. Med. 2011;365:2277-86).

In a subgroup analysis involving only the 51 subjects who were most compliant with CPAP, with a mean use of at least 5 hours every night, the improvements in components of the metabolic syndrome were even greater. In particular, systolic BP decreased by 5.6 mm Hg and diastolic BP decreased by 3.3 mm Hg. This subgroup of patients also showed significant improvement in carotid intima-media thickness.

This study was funded by Pfizer. All investigators reported having no financial conflicts of interest. They received technical support from ResMed Corp. in designing a sham CPAP machine. ■

COMMENTARY

Dr. Paul Selecky, FCCP, comments: We have known for some time that successful CPAP use for OSA has resulted in a decrease in insulin resistance and improvement in other parameters of diabetes management. Similar results have been found in improving hypertension. Adding improved metabolic syndrome to the list is therefore not surprising, but is important information nonetheless. These findings emphasize yet one more benefit that can come from the CPAP treatment of OSA.

TYGACIL is in the IDSA/SIS guidelines for cIAI and the SIS guidelines for cSSSI.[1,2]

Expanded broad-spectrum coverage[3]* is on your side

***TYGACIL does not cover *Pseudomonas aeruginosa*.**

TYGACIL is indicated for the treatment of adults with:

- **Complicated skin and skin structure infections** caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*
- **Complicated intra-abdominal infections** caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*
- **Community-acquired bacterial pneumonia** caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*

Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options**
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.** TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, infection, headache, and abdominal pain
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary of Prescribing Information on adjacent page.

References: 1. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133-164. **2.** May AK, Stafford RE, Bulger EM, et al. Surgical Infection Society Guidelines: Treatment of complicated skin and soft tissue infections. *Surg Infect*. 2009;10:467-499. **3.** TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.

Pfizer

Tygacil® tigecycline IV

Expanded broad-spectrum coverage