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.

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

Complaints Influence Final Rule on ACOs

BY ALICIA AULT
Elsevier Global Medical News

Use of electronic medical records is no longer a condition for receiving the Medicare meaningful use incentive payments, 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.

"Thinking about a change? Interested in relocating? Go where the jobs are ..."
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-vein-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-vein-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 0.50% 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 as 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 co-investigators 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 with the ARISTOTTLE 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/NEJMoai110899). Dr. Goldhaber has served as a consultant to numerous pharmaceutical companies, including Bristol-Meyers Squibb and Pfizer, who sponsored the ADOPT trial. Dr. Antman and Dr. Cushman declared no relevant financial interests.
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 CaV enT 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 CaV enT (Catheter-Directed Thrombolysis for Acute Illofemoral 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.

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 CaV enT trial, but results from the North American trial are not expected until 2015.

CaV enT randomized 209 patients at 20 hospitals in Norway with the acute illofemoral 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 illofemoral patency at 6 months from 47.4% with standard therapy to 65.9% (P = .012), Dr. Sandset said.

Importantly, patients who regained illofemoral patency at 6 months had significantly less PTS at 2 years than those who experienced insufficient recanalization (36.9% vs. 61.3%, P < .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 illofemoral DVT and no apparent risk of bleeding,” he 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 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 patients 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 approach pioneered previously 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.

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 and fluid accumulation. “I think it is 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).

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 cardiovascualr 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 submssive 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,
exposing plasminogen receptor sites. Thrombus permeability and thrombolytic penetration are dramatically increased. Ultrasound 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/UV 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.

**A primary goal of COPD management**

Severe COPD patients are at a higher risk

Recent studies have shown that the frequency of exacerbations increases as COPD becomes more severe.\(^5,11\) In fact, the recent ECLIPSE study demonstrated that patients with severe or very severe COPD had a greater likelihood of experiencing COPD exacerbations. This study also found that the best predictor of a future exacerbation is a history of previous exacerbations.\(^1\)

![Exacerbation Frequency by GOLD COPD Stage](image)

**Patients with severe and very severe COPD and a history of exacerbations are also at greater risk for hospitalizations due to an exacerbation**


**Preventing exacerbations is a primary goal of COPD management**

Thanks for making CHEST and CHEST Physician the top 2 publications read by pulmonologists! (Kantar Media Medical/Surgical Readership Study, December 2011)
Asthma Drugs in Pregnancy

Christina Chambers, Ph.D., M.P.H.

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 information 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 increased. 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 other factors. Continued on following 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 non-inhalational drugs suggests that perhaps women on polytherapy had more optimum treatment and therefore better control. The second study used a retrospective cohort design and analyzed data collected between 1990 and 2002 in the US. The 13,117 pregnancies selected for the analysis were limited to those with a coded diagnosis of asthma and were excluded from orofacial clefts patients and from the replication of adult cases in the year before pregnancy. The exposures evaluated were any prescription in the periconception period for long-acting beta-agonists, for rescue medication (such as albuterol), and any prescription in the periconception period for a long-acting beta-agonist, against controller medication (such as inhaled corticosteroids) for asthma, as available during the years the study was conducted as a single active ingredient medication.

In all, 17 categories of major congenital malformations were evaluated as described above, including orofacial clefts, and only 2% 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-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-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-agonists, as the authors point out, could be influenced by the higher rate of more severe and less well-controlled asthma among these women who reduced or discontinued their prescribed medication. If this trend occurs, it may reflect a rise in non-prescription use of long-acting beta-agonists. The authors concluded, however, that the increased risks described are very small and should not eliminate the use of long-acting beta-agonists for asthma control, as these drugs provide significant benefits for asthma control, which in turn may reduce the risk of asthma morbidity and mortality.

ASSESSMENTS: The study provides new evidence for the importance of asthma control in pregnancy and supports the use of long-acting beta-agonists for asthma control in pregnancy. Further research is needed to better understand the mechanisms underlying these findings and to confirm the results in other populations.
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, he said, 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 beta2 agonists and long-acting antimuscarinics. Other agents in development include bifunctional muscarinic antagonist-beta2-agonist combinations of once-daily long-acting beta2-agonist 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.

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.
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 report recommends. 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.

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odified-risk tobacco products – such as 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 recommends.

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 FEDs on the design and conduct of scientific studies of modified-risk tobacco products.

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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 recommends. 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.

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 recommends. 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.

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The following is a brief summary of the full prescribing information for TYVASO® (treprostinil) for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness involved predominantly patients with PAH secondary to scleroderma. Class IIa evidence and strong clinical need and no other treatment options were associated with treatments for PAH (2012). The effects observed during the minimum recommended dosing interval of 12 hours, treatment time can be adjusted for clinical situations. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or iloprost (a phosphodiesterase type 5 inhibitor). The controlled clinical experiences was limited to 12 weeks in duration.

CONTRIBUTIONS

In

WARNINGs AND PRECAUTIONS

Patients with Pulmonary Artery or Pulmonary Hypertension:
The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with severe pulmonary hypertension should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Effect of Other Drugs on TYV

ASO—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may precipitate a hypotensive episode. Patients with history of or family history of hypertensive disease are more likely to develop systemic hypertension. Tyvaso is contraindicated in these patients. Patients with hypertension or hemodynamic instability are at greater risk for systemic hypotension.

Adverse Events

Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent* than Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Rash</td>
<td>45 (34)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Infections</td>
<td>29 (25)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Edema</td>
<td>22 (18)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11 (9)</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td></td>
</tr>
</tbody>
</table>

More than 10% greater in patients treated with TYVASO compared to placebo.

More than 10% greater in patients treated with TYVASO compared to placebo.

The safety of TYVASO was also studied in a 13-week, open-label, extension study in which 256 patients were dosed for a mean duration of one year. The adverse events observed in this chronic dosing study were generally similar to those observed in the 12-week placebo controlled trial. Adverse events associated with bosentan (ORALIN®) in the trial group during the double-blind and open-label phase including initiation in the placebo treated group included: cough, throat irritation, pharyngitis, rash, exanthem and flushing. Serious adverse events during the open label portion of the study included pneumonia in 1 patient. There were three serious episodes of hemorrhage (new site bleeds) during the open-label experience.

DOSAGE INTERACTIONS

Pharmacokinetic/Pharmacodynamic interactions have not been conducted in clinical trials of TYVASO. Some of such studies have been conducted with bosentan (a phosphodiesterase type 5 inhibitor) and subcutaneously administered treprostinil (Endelin®). No pharmacokinetic/ pharmacodynamic interactions have been observed when treprostinil is administered to patients with renal insufficiency.

ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions:

• Decrease in systemic blood pressure
• BLEEDING

Pharmacokinetic studies in healthy subjects have shown that treprostinil does not inhibit cytochrome P450 3A4 (CYP3A4) and 2C8 (CYP2C8) isoenzymes. Treprostinil does not induce these isoenzymes. Treprostinil is metabolized by human liver cytochrome P450 3A4 (CYP3A4) and 2C8 (CYP2C8). Treprostinil is administered by the inhalation route. However, studies in preclinical animals using continuous subcutaneous (i.v.) or intranasal treprostinil at doses higher than the maximum human dose indicate that the pharmacokinetics of treprostinil may be influenced by interaction of treprostinil with human cytochrome P450 isoenzymes.

There were no clinically significant drug interactions observed in clinical trials of TYVASO including co-administration of CYP2C8 enzyme inhibitor (e.g., gemfibrozil) with treprostinil. Treprostinil does not induce CYP2C8, and the pharmacokinetics of treprostinil did not change when treprostinil was co-administered with gemfibrozil. Treprostinil is administered by the subcutaneous route. Data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or iloprost (a phosphodiesterase type 5 inhibitor). The controlled clinical experiences was limited to 12 weeks in duration.

CONTRAINDICATIONS

There are no contraindications for TYVASO for the treatment of PAH. However, treatment should be initiated with caution in patients with moderate to severe heart failure, unstable angina pectoris, recent MI, uncontrolled hypertension, or symptomatic hepatic, renal, or cardiac dysfunction.

Infection Risk

The infection risk of TYVASO is quite reactive,” causing fevers and local reactions, she said in an interview. “At this point, we would not accept the whole-cell vaccine,” she said. Possible options include additional boosted vaccines, or moving administration of the first 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 event of time elapsed following the fifth dose relative to when pertussis infection occurred showed that after about 5 years the vaccine efficacy was 71% below where it stood immediately after the fifth dose, reported Lara K. Misegades, Ph.D., an epidemiologic 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 fifth dose compared to children who received their fifth doses after 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 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 delivery of the fifth dose. (See table.)

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

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.”

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NAVA (Neurally Adjusted Ventilatory Assist) improves asynchrony with closed loop technology that links patient effort to ventilator support. With SERVO-i and NAVA, clinicians have an intuitive breakthrough tool for:

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- Intuitive feedback for successful Spontaneous Breathing Trials
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VISIT VENTILATIONSYMPOSIUM.COM TO REGISTER FOR THE FEBRUARY 4TH SYMPOSIUM, HOUSTON, TEXAS AT SCCM 2012, VISIT MAQUET BOOTH #709
Starting Dates Pushed Back
ACOs • from page 1

“When folks see the rules and see the many changes, they will see that CMS listened,” said 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 weighed 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 allowed 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, including 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 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 ACOs understand how to comply with the rules.

In the proposed rule, ACOs 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 would receive 52% of payments, a savings outlier payment; or a monthly payment of varying amount depending on 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 antitrust 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.

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

Daliresp® (roflumilast) tablets 500 mcg

COPD=chronic obstructive pulmonary disease.
**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](http://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 exacerbations¹,²

- Reduces moderate or severe exacerbations by 17% vs placebo¹,³,⁴
- Effective alone or in combination with a bronchodilator¹,³
- Effective in older and younger patients (>65 and 40-65 years)¹,³
- Statistically significant increase in lung function (pre-bronchodilator FEV₁) of 48 mL vs placebo¹,⁴
  - DALIRESP is not a bronchodilator; this increase was not clinically significant¹,³
- The first class of drugs approved for COPD in 25 years²,⁵

• 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

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 FEV₁) were co-primary endpoints. Each study met both co-primary endpoints.

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

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.

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

**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 FEV₁) 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

**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.
DALRESP™ (roflumilast) tablets  Rx Only  

**Brief Summary of full Prescribing Information**

**Initial US Approval**  
2011

**INDICATIONS AND USAGE**

DALRESP™ 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**

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

**CONTRAINDICATIONS**

The use of DALRESP 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**

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

**Psychiatric Events Including Suicidality**

Treatment with DALRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (283) of patients treated with DALRESP 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 DALRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [see Adverse Reactions (6.1)]. Incidences 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 DALRESP compared to one patient (completed suicide) who received placebo. Before using DALRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALRESP 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 DALRESP if such events occur.

**Weight Decrease**

Weight loss was a common adverse reaction in DALRESP clinical trials and was reported in 7.5% (321) of patients treated with DALRESP 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 lost during treatment. Patients treated with DALRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALRESP should be considered.

**Drug Interactions**

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by VYP6•3 and VYP%•2 simultaneously [see Drug Interactions (5.4) 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 (5.3)]
- **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 clinical practice. The safety data described below reflect exposure of 336, patients to q•L–RHSP 0.99 mcg once daily in four year placebo-controlled trials [see Clinical Studies (7.1) and Clinical Pharmacology (12.3)].

The incidence of adverse reactions was assessed on a case-by-case basis at a maternal dose of 0.2 mg/kg/day during pregnancy and lactation. DALRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRH (an mg/kg/day basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

**Labor and Delivery**

DALRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALRESP on breast-fed infants. DALRESP should not be used by women who are nursing.

**Pediatric Use**

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

**Use in Specific Populations**

**Geriatric Use**

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 clinical practice. The safety data described below reflect exposure of 336, patients to q•L–RHSP 0.99 mcg once daily in four year placebo-controlled trials [see Clinical Studies (7.1) and Clinical Pharmacology (12.3)].

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**Nursing Mothers**

DALRESP should not be used by women who are nursing.

**Neonates and Pediatric Use**

Pediatric use of DALRESP in children has not been established.

**Concomitant Use with CYP3A4 Inhibitors**

Concomitant use of DALRESP with strong CYP3A4 inhibitors 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 DALRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol 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)].

**USE IN SPECIFIC POPULATIONS**

**Hepatic Impairment**

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment (Child-Pugh A and B subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 91% and 24%, respectively in Child-Pugh A subjects by 92% and 25%, respectively in Child-Pugh B subjects as compared to healthy subjects. The Cmax of roflumilast and roflumilast N-oxide were increased by 49% and 36%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. In a single dose study, 500 mcg has not been studied in specifically impaired patients. Clinicians should consider the risk/benefit of administering DALRESP to patients who have mild liver impairment (Child-Pugh A), DALRESP 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 Cmax 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 DALRESP. During the Phase I studies of DALRESP the following symptoms were noted after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadiness, 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, its drug interaction analysis is not likely to be an efficient method of drug release. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

**Manufactured by:**

Nycomed GmbH  
Production Site Dranenburg  
Lehnitzstrasse 70 – 98  
31515 Dranenburg  
Germany

**Manufactured for:**

Farrell Pharmaceuticals, Inc.  
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St. Louis, MO 63045, USA  
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Please also see full Prescribing Information at www.dalresp.com.
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 forums and grounds for the dissemination of medical information to a closely knit community.

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 $8 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 expansion 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 Overholt (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 tuberculosis’ 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 for video and 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, 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 announced 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 lunchtime panels and evening fireside conferences were conceived and offered. The informal small focus groups were interactive, allowing all present to partake in the discussion. The ACCP 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 smoke-designated areas, attracting national attention and public media. At the same time, the committee on Smoking and Health emuncted 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 Ebola 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 Dellar, 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 national 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.
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 Category 1 Credit™, which is used by state licensing boards and boards of medical specialties to relicence 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 performance
- 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

This recognition demonstrates the collaboration of 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.

Accreditation With Commendation for the ACCP
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. He is also an Associate Professor 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.

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 is a 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.

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.

Dr. David Schulman, 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 NAMDRF. 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.

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.

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.

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.

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.

ONEBreath
Make The Most Of It*

The CHEST Foundation is pleased to introduce OneBreath, an exciting campaign that inspires people to take care of their lungs and heart, never taking their next breath for granted.

OneBreath incorporates the resources of The Foundation and extends its reach to the public. Under the three pillars of education, care, and community, it offers a breadth of content, from patient education materials to prevention and wellness tips. When you become a member of OneBreath, you gain access to the OneBreath resources, including a calendar for viewing and planning lung health outreach events in your community.

Learn More and Join the Online Community OneBreath.org
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.

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.

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

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

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

Our new FCCPs standing proudly on the dais.

CHEST 2011 Sessions Available for Purchase

- Hear the Sessions You Missed
- Listen to Sessions Again

Purchase the CHEST 2011 sessions package, a Web-based, full-motion video with synced audio narration. The video includes the audio and slides from the session presentations, showing mouse movements used by speakers, slide animations and builds, and embedded videos. Approximately 80% of the sessions were recorded and are included with one purchase price. Significant discount for CHEST 2011 attendees.

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Simulation Education. Real Results.

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2012 Courses

Four Hands-on Opportunities.

Don’t Miss These Sessions

- Fundamentals of Airway Management: Skills, Planning, and Teamwork
  March 8 - July 19
  Northbrook, IL

- Difficult Airway Management: A Critical Care Approach
  March 9-11 - July 20-22
  Northbrook, IL

- Fundamentals of Mechanical Ventilation for Providers
  February 23
  Northbrook, IL

- Mechanical Ventilation: Advanced Critical Care Management
  February 24-26
  Northbrook, IL

Learn more and register.
www.chestnet.org/simulation

- Take one course to advance your skills in a specific area.
- Take multiple courses to meet the requirements for the Airways Management or Mechanical Ventilation Certificate of Completion Programs.
Congratulations to the Many Winners at CHEST 2011

ACCP Honor Awards
- Alfred Sofer Award for Editorial Excellence
  Michael B. Zack, MD, FCCP
- Allen Oehmker 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 McCaffre, MD, Master FCCP, Humanitarian Award
  $1,500 Award
  Thomas R. Gill, MD, FCCP
  Thomas Lahiri, MD, FCCP
  Sanjay P. Desai, MD, FCCP
  $10,000 Ambassadors Group Award
  Peter Karczmar, MD, FCCP
  $5,000 Award
  Raghu R. Sundaram, MBBS
- Alpha-i Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-i Antitrypsin (AAT) Deficiency
  Andrew John Sandfor, 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
- OneBreathTM Clinical Research Award in Lung Cancer
  Sairkshna S. Vendamuri, MD, FCCP

Alfred Sofer Research Award Winners
$1,000 Award Winners
- Said Haque, MD
- Dixie Harris, MD
- Randall Keyser, PhD
- Vickie Shannon, MD

$1,000 Award Winners
- Muhammad Akbar, MD
- Jared Chiarchiari, MD
- Masafumi Matsui, MD
- Alexandra Quittner
- Norhu Shigemura, MD

Case Report Awards
- Mohammad Syed, MD, MBBS
- Satish Chandrashekaran, MD
- Amanda Godfrey, MD
- Richard Patch, MD
- Amir Emerjoojoo, MD, MSc
- Annie Harrington, MD
- Rabih Halabi, MD
- Sean Roark, MD
- Darlene Nelson, MD
- Naveed Hasan, MBBS
- Allison Cihla, MD
- Jimmy Susantine, MD
- Angel Cox Yaraco, MD
- Choo Khoon Ong, MD
- Matthew Aboudouar, MD
- Michael Lampa, MD
- Adam Wellikoff, MD
- Melhem Imad, MD
- Gregory Waiterek, MD
- Tathagat Narula, MD, MBBS
- Christine Gould, MD
- Rahat Hussain, MD
- Maher Ghamlouhsh, MD
- Mingjen Kuo, MD
- Tathagat Narula, MD, MBBS

Dr. Rajat Kapoor from Troy, Michigan, was the winner of The CHEST Foundation’s OneBreath iPad 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.
A s 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 (Sowers Arch Women’s Health. 2005;8:207). 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 increased progesterone levels (Manber and Bootzin. Health Psychol. 1997;16[3]:209).

Data now exist on female sleep during pregnancy than during any other phase of the female life cycle. The vast majority of women who were pregnant 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. Obstet. Gynecol. 2000;101[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 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;96[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 preganadel glucuronide, a progesterone metabolite, was a better marker for predicting trouble sleeping during the perimenopausal period (Krivitz 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]:125). 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[6]: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.

In Remembrance

Brian J. Whipp, PhD, DSc, died on October 20, 2009, at the University of Wales Hospital in Cardiff, Wales, United Kingdom.

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 becoming Professor of Physiology and Medicine and Vice-Chairman of UCLA’s Department of Physiology. During this period, he was awarded an Established Investigation 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

- Nonspecific Interstitial Pneumonia: A Review Article. By Dr. Mary E. Strek, FCCP, and Dr. Imre Noto, 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. Oliver, Dr. Danielle Antin-Ozerkis; and Dr. Ami N. Rubinowitz
2011 Centers of Excellence Enjoyed by Attendees

O n 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 garner 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 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. Martindik, MD, FCCP

“Our not-for-profit, Not One More Life, Inc (NOML) (www.nomorelife.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.
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 our clinicians 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.

Apopotosis 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 Ballestro
Dr. Vincenzo Savarino

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Pulmonology/Critical Care Physicians

Practice Opportunity for BC/BE Pulmonology/Critical Care Physicians in Beautiful Hendersonville, Western North Carolina. Sleep Medicine preferred but not required. Full-time or Part-time available. Competitive salary & benefits. No Visa sponsorship available. For consideration e-mail CV to: lilly.bonetti@pardeehospital.org or Fax CV to 828-694-7722.
CPAP Reduced Metabolic Syndrome in OSA Patients

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 mellitus. The data from the current study supports these findings.

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 trypglycerides plus HDL cholesterol in one; and improved triglycerides, HDL cholesterol, and fasting blood glucose in one.

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 mg/Hg, a mean decrease in diastolic BP of 2.5 mg/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 point to a decrease in daytime somnolence and a consequent increase in physical activity.

COMMENTARY

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In a subgroup analysis involving only the 51 subjects who were most compliant with CPAP use, the improvements in components of the metabolic syndrome were even greater. In particular, systolic BP decreased by 5.6 mg/Hg and diastolic BP decreased by 3.3 mg/Hg. This subgroup of patients has shown significant improvement in carotid intima-media thickness.

This study was funded by Pfizer. All investigators reported having no financial conflicts of interest.

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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 group (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 group (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-arabolic 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.