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CATHERINE HARRELL/ELSEVIER GLOBAL MEDICAL NEWS

Women with severe SDB had an adverse pregnancy outcome rate of 38.5%, compared with 18.1% in those without SDB.

Sleep Apnea May Affect Birth Outcome

BY DIANA MAHONEY
Elsevier Global Medical News

MINNEAPOLIS – Women with sleep-disordered breathing have an increased likelihood of adverse pregnancy outcomes, but it is unclear whether the heightened risk can be attributed primarily to the breathing disorder or to obesity, reported lead investigator Dr. Francesca L. Facco.

Sleep disordered breathing (SDB) occurs in approximately 2% of the female population and has been linked to cardiovascular and metabolic morbidities and mortality in nonpregnant populations, said Dr. Facco of Northwestern University in Chicago. However, "few studies have examined the relationship between abnormal respiratory patterns or quality of ventilation during sleep in pregnancy and adverse obstetrical outcomes, which is what we sought to do in this investigation," she said at the annual meeting of the Associated Professional Sleep Societies.

Toward this end, Dr. Facco and her colleagues conducted a retrospective cohort study, using ICD-9 codes to identify women who had a delivery and an in-laboratory polysomnogram at their institution between January 2000 and June 2009. They reviewed the medical charts of 150 patients and abstracted data on demographics, sleep study results, and pregnancy outcomes.

The study's primary outcome was adverse pregnancy outcome, which was defined as pregnancy-induced hypertension, gestational diabetes, and early preterm birth (at or before 34 weeks' gestation), Dr. Facco said. The apnea-hypopnea index (AHI) was used to classify the presence and degree of SDB, with an AHI of fewer than 5 breathing pauses per hour indicating no SDB, an AHI of 5-14.9 pauses per hour indicating mild to moderate SDB, and an AHI of 15 or more pauses per hour suggesting a severe condition, she said.

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Molecular Profiling Transforming Lung Cancer Care

'Progress has been so dramatic.'

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – Management of advanced non–small cell lung cancer now demands molecular profiling and personalized treatment. This new era has just begun, but it will quickly transform the field over the next 4 years, Dr. David R. Gandara said in a talk on the state of lung cancer medical oncology.

Increased molecular profiling – Dr. Gandara called for routine molecular profiling for every patient with advanced NSCLC – will mean a "culture change" for the field, and a sharp turn toward "ungrouping" the universe of NSCLC patients into individuals, he told attendees at the World Conference on Lung Cancer, which was sponsored by the International Association for the Study of Lung Cancer.

"We shouldn't even talk about non–small cell lung cancer" as though it were a single entity, said Dr. Gandara, professor and director of the thoracic oncology program at the University of California, Davis, Cancer Center in Sacramento.

He also recommended new paradigms of drug development to reflect the complex underlying biology and the inter- and intrapatient heterogeneity of lung cancer. "Transition from empiric to rationally selected and personalized therapy is challenging," Dr. Gandara conceded. But the transition is underway and accelerating.

Until about a year ago, the only lung cancer genes undergoing routine profiling at cancer centers were those for the epidermal growth factor receptor (EGFR) and, at fewer locations, for the oncogene KRAS. Dr. Bruce Johnson, who is a professor of medicine

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INSIDE

RSV, Rhinovirus Coinfections Common

BY MIRIAM E. TUCKER
Elsevier Global Medical News

BOSTON – Coinfections with both respiratory syncytial virus and rhinovirus were common and associated with increased length of stay in a prospective multicenter study of more than 2,000 children under 2 years of age who were hospitalized with bronchiolitis.

The clinical value of testing for an infectious etiology in a child with bronchiolitis is unclear. Indeed, the recommendation is not to test (Pediatrics 2006;118:1774-93). Some argue however, that testing may be useful for the influenza treatment or to identify the beginning of the viral "seasons" and which viruses are circulating, Dr. Jonathan M. Mansbach, of Children's Hospital Boston, said at the annual meeting of the Society for Academic Emergency Medicine.

Additionally, Dr. Mansbach said that the 70% frequency of coinfection seen in this study raises questions about the effectiveness of inpatient cohorting by viral etiology,

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Sleep Apnea Screening Inadequate in Pregnancy

BY DIANA MAHONEY
Elsevier Global Medical News

MINNEAPOLIS – A two-question screening tool for sleep apnea yielded more accurate results than did standard screening tools, a study has shown.

"Using prepregnancy body mass index and self-reported snoring had a much better sensitivity than the conventional methods, without sacrificing much specificity," Dr. Francesca L. Facco reported at the annual meeting of the Associated Professional Sleep Societies.

In a cohort of pregnant women who completed a sleep survey and participated in an overnight sleep evaluation, the two-question screening approach yielded more accurate results than did standard screening tools, including the Berlin Questionnaire (BQ) and the Epworth Sleepiness Scale (ESS), she said.

To compare the screening approaches, Dr. Facco of Northwestern University, Chicago, and her colleagues recruited 86 high-risk pregnant women, including those with chronic hypertension, pregestational diabetes, obesity, or a prior history of preeclampsia, to complete the sleep survey, which consisted of the BQ and ESS measures.

The women also underwent an overnight sleep evaluation using Itamar Medical's Watch-PAT100 (WP100), a wrist-mounted, ambulatory device designed to diagnose sleep apnea, Dr. Facco said.

For this study, sleep apnea was defined as an apnea-hypopnea index score of five or more episodes of disturbed sleep per hour.

Patients' prepregnancy BMI and self-reporting snoring status were recorded as well.

"Patients with a prepregnancy BMI of 25 [kg/m^2] or higher who also reported snoring were considered to be screen positive" for apnea, Dr. Facco said.

The investigators assessed the performance of the BQ, ESS, and two-question measures relative to the data acquired from the WP100 devices using receiver operating characteristic (ROC) curves, and determined that the two-question approach performed better than the BQ alone, the BQ and ESS combined, and the null hypothesis, according to Dr. Facco.

The sensitivity of the combined BQ and ESS was 35% and the specificity was 69%, compared with 74% and 59%, respectively, for the two-question approach. "The results suggest that standard screening tools for sleep apnea, which have a high sensitivity and specificity in nonpregnant individuals, are inadequate for the assessment of sleep apnea in pregnancy," Dr. Facco said.

Modifications that take into account the predictive value of prepregnancy BMI and snoring are warranted, she said, stressing that additional studies are needed to design and test the most appropriate measure for sleep apnea screening in pregnancy.

Because sleep apnea may be associated with complications during pregnancy and with adverse pregnancy outcomes, screening for the disorder should be considered for all pregnant women, and particularly those who are considered to be at high risk, Dr. Facco said.

Dr. Facco had no relevant financial conflicts of interest. ■

COMMENTARY

Dr. Paul Selecky, FCCP, comments: Snoring during pregnancy has many possible causes, including obesity, nasal congestion, and the soporific effects of the alteration in hormones. When it goes undetected and, therefore, untreated, sleep apnea carries a number of significant pregnancy-related adverse effects, including low birth weight, pre-elampsia, gestational diabetes, hypertension, and early preterm birth. It is important to educate and urge our obstetric colleagues to ask patients about snoring, and if it is present, to address it appropriately.

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More Preterm Births

Apnea • *from page 1*

The associations between SBD and adverse pregnancy outcomes were evaluated using a chi-square test for trend.

Of the 150 women included in the investigation, 61% were nulliparous at the time of their first documented delivery at the study hospital, 72% had undergone a polysomnogram within 3 years of their delivery, and 86.7% were overweight or obese (defined as a body mass index of 25 kg/m^2 or greater) at the time of delivery, Dr. Facco reported.

An analysis of the findings found a significant association between SDB and adverse pregnancy outcome. "The incidence of adverse pregnancy outcomes was highest in women with severe sleep apnea," she said, noting that the increased prevalence was principally driven by a higher incidence of gestational diabetes and early preterm birth.

In the no, mild, and moderate to severe SDB groups, respectively, the researchers found the following:

- The composite adverse pregnancy outcome rates were 18.1%, 23.5%, and 38.5%.
- The gestational diabetes rates were 0%, 5.9%, and 11.5%.
- The preterm birth rates were 4.7%, 5.9%, and 15.4%.
- The pregnancy-induced hypertension rates were 16.9%, 17.6%, and 15.4%.

"In this population, nearly 87% of the women who had [SDB] were also obese, making it an obvious confounding factor," Dr. Facco said in an interview.

Further prospective studies are needed to assess the independent impact of SDB on maternal and neonatal health, and if the independent association is confirmed, additional studies on the role of treatment in pregnancy would be needed, Dr. Facco said.

Dr. Facco said she had no relevant disclosures. ■

CHEST PHYSICIAN

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Daily Azithromycin Prevents COPD Exacerbations

'Adding azithromycin ... is a valuable option.'

BY MARY ANN MOON
Elsevier Global Medical News

Daily azithromycin prevented acute exacerbations of chronic obstructive pulmonary disease when it was added to usual treatment in a 1-year study, thus improving patients' quality of life.

The drug also cut the colonization of certain respiratory pathogens. On the downside, it increased colonization with macrolide-resistant organisms and induced hearing decrements in approximately 5% of patients, said Dr. Richard K. Albert, FCCP, professor of medicine at the University of Colorado at Denver and chief of medicine at Denver Health, and his associates.

"Given the deleterious effects of acute exacerbations of COPD with respect to the risk of death, quality of life, loss of lung function, and cost of care, adding azithromycin to the treatment regimen [of at-risk patients] is a valuable option," they noted.

However, QTc prolongation is a contraindication to the drug, and patients who are at risk for the cardiac disorder should be monitored if they are given azithromycin. Hearing also should be monitored in all patients. "In addition, it should be recognized that the long-term effects of this treatment on microbial resistance in the community are not known," the investigators said.

Macrolide antibiotics like azithromycin have immunomodulatory and anti-inflammatory properties in addition to their antibacterial action. Several small studies have examined their use in preventing acute exacerbations of COPD, with conflicting results. "Accordingly, we conducted a large, randomized trial to test the hypothesis that azithromycin decreases the frequency of acute exacerbations of COPD when added to the usual care of these patients," said Dr. Albert and his colleagues in the COPD Clinical Research Network.

VITALS

Major Finding: Adding oral azithromycin (250 mg daily) to usual care for COPD increased the time to an acute exacerbation from 174 days to 266 days, and reduced the frequency of acute exacerbations.

Data Source: A 1-year prospective, multicenter, randomized clinical trial involving 1,142 patients at risk for COPD exacerbations.

Disclosures: This study was funded by the National Heart, Lung, and Blood Institute and the COPD Clinical Research Network. Dr. Albert reported ties to Gilead Sciences, the Bruce Fagel Law Firm, Elsevier, and Denver Health, and his associates reported ties to numerous industry sources including Pfizer, marketer of Zithromax.

The prospective study involved 1,142 patients aged 40 years and older who were at risk for acute exacerbations and were randomly assigned to receive either 250 mg of oral azithromycin (570 subjects) or an identical-looking placebo (572 subjects) once daily for 1 year. All were already using inhaled glucocorticoids, long-acting beta-agonists, muscarinic antagonists, and/or continuous supplemental oxygen.

These subjects were followed at 17 sites associated with academic health centers across the United States.

The primary outcome measure – time to the first acute exacerbation of COPD – was significantly increased in the patients taking azithromycin (266 days), compared with those taking placebo (174 days). The hazard ratio of having an acute exacerbation per patient-year was 0.73 in the azithromycin group, compared with the placebo group.

These differences remained significant after the data were adjusted to account for differences between the two groups in sex, forced expiratory volume in 1 second (FEV_1), age, and smoking status, the researchers said (N. Engl. J. Med. 2011;365:689-98).

There were 1,641 acute exacerbations of COPD during the study, and the number was significantly lower in the active-treatment group (741) than in the placebo group (900). "The number needed to treat to prevent one acute exacerbation of COPD was 2.86," they said.

More patients in the azithromycin group than in the placebo group showed significant improvements in quality of life scores.

There were no significant differences between the two groups in the frequency of serious adverse events or of adverse events that prompted discontinuation of treatment. Audiograms showed hearing decrements in 25% of patients taking azithromycin, compared with 20% of those taking placebo.

Among study subjects whose nasopharyngeal swabs showed colonization with respiratory pathogens at baseline, the later prevalence of organisms that were resistant to macrolides was comparable whether they took azithromycin or placebo. In contrast, among subjects who became colonized during the study, the rate of macrolide resistance was twice as high in those taking azithromycin (81%) as in those taking placebo (41%).

Dr. Albert and his associates added that they chose the 250-mg dose of azithromycin to minimize the chance of insufficient dosing, and chose daily rather than less-frequent administration to maximize adherence. "It is possible that lower doses or less frequent administration could have produced similar results," Dr. Albert and his colleagues said. ■

Dosing Schedule, Safety Data Updated for Varenicline

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

An updated label for the smoking cessation drug varenicline that includes new safety data for people with cardiovascular disease has been approved by the Food and Drug Administration, the agency has announced.

Also added to the label is information on the use of varenicline in patients with COPD and alternative directions for selecting a date to quit smoking, according to the announcement. Varenicline, a nicotinic receptor partial agonist, was approved in 2006 for use as an aid to smoking cessation treatment; it is marketed by Pfizer as Chantix.

The cardiovascular safety information summarizes the results of a randomized study of 700 smokers with stable cardiovascular disease who received 1 mg of varenicline twice a day or placebo for 12 weeks and who were followed for an additional 40 weeks. The study found that those on varenicline had twice the chance of staying abstinent from smoking for as long as 12 months, compared with those on placebo. But it also found that treatment "may be associated with a small increased risk of certain cardiovascular adverse events in these patients."

Physicians are advised to "always weigh the potential benefits of Chantix against its potential risks when deciding to use the drug in patients with cardiovascular disease."

In a safety alert issued by the FDA, the agency stated that over 52 weeks, there were more reports of certain cardiovascular events among those on varenicline, compared with those on placebo. Those events included nonfatal myocardial infarction (2% vs 0.9%) and the need for coronary vascularization (2.3% vs. 0.9%). The information on patients with COPD summarizes the results of a 52-week study of 460 patients with mild to moderate COPD, aged 35 years and older, that found that treatment with varenicline, 1 mg twice daily for 12 weeks, was more effective in helping these patients quit smoking and stay abstinent for as long as 1 year, when compared with placebo.

The varenicline label has advised that patients select a date to quit smoking and start taking varenicline 7 days before that date. The label still includes that recommendation, but now states that as an alternative, patients can start taking varenicline "and then quit smoking between days 8 and 35 of treatment."

That recommendation is based on the results of a randomized study of otherwise healthy smokers that found the alternative dosing schedule was more effective than placebo in helping patients quit smoking and remain abstinent for as long as 24 weeks.

The potential cardiovascular risks associated with varenicline received widespread media coverage in July with the online publication of a meta-analysis of 14 studies comparing the drug to placebo (Can. Med. Assoc. J. 2011 July 4 [doi:10.1503/cmaj.110218]).

The studies enrolled more than 8,000 patients, including almost 5,000 on varenicline (most were taking the 1 mg twice a day dose), treated for 7-52 weeks. Patients with cardiovascular disease were included in the trials, but all but one excluded those with unstable cardiovascular disease. The rate of serious cardiovascular events was significantly higher among those on varenicline compared with placebo (1.06% vs. 0.82%), which represented a 72% increased risk.

While the study had some limitations, it did raise safety concerns about the potential for these events in people treated with the drug and follow-up safety studies should be conducted, the authors concluded.

In an editorial, Dr. J. Taylor Hays, of the Mayo Clinic, Rochester, Minn., wrote that "the small absolute risk of cardiovascular events associated with taking varenicline is outweighed by the enormous benefit of reducing cardiovascular morbidity and mortality that can be achieved with successful abstinence from smoking" (Can. Med. Assoc. J. 2011 July 4 [doi:10.1503/cmaj.110804]).

Dr. Hays has received grant funding from Pfizer to conduct a varenicline study. The lead author of the meta-analysis, Dr. Sonal Singh, of Johns Hopkins University, Baltimore, was supported with a grant from the National Center for Research Resources, a component of the National Institutes of Health.

COMMENTARY

Dr. Stuart Garay, FCCP, comments: Varencline is one the few pharmacologic agents available for smoking cessation. Nonetheless, attention must be paid to potential serious side effects in certain patient populations. As always, all drugs carry a risk:benefit ratio. First, do no harm.

A statement issued by Pfizer said that the company is discussing with the FDA a protocol for a meta-analysis of Pfizer's clinical trial data to evaluate the drug's cardiovascular risk. Pfizer's statement also says that the company stands by the risk-benefit profile of varenicline, and expressed concerns about the reliability of the meta-analysis. The company's stated concerns included the way cardiovascular events were counted and the small number of events that were the basis of the conclusions. ■

POINT/COUNTERPOINT

Should Nebulized Hypertonic Saline Be Used in the Treatment of Acute Viral Bronchiolitis?

Nebulized hypertonic saline is an emerging therapy for this indication.

SHAWN RALSTON, M.D.

Viral bronchiolitis is the most common diagnosis at hospitalization for infants younger than 1 year of age.

It results in approximately 150,000 hospitalizations each year at a cost of more than $500 million, according to a study published in 2006 (Pediatrics 2006;118:2418-23). Yet so far, nothing we give our patients really works.

Nebulized hypertonic saline is garnering enthusiasm because there is a consistent set of papers and a theory of physiology supporting its efficacy in the treatment of acute viral bronchiolitis.

The very first hypertonic saline study came from a group of Israeli pulmonologists who reported an improvement in symptoms and respiratory scores on day 2 of inhaled nebulized 3% saline solution plus 5 mg terbutaline in 33 outpatient infants with viral bronchiolitis, compared with 32 control infants who received 0.9% saline plus 5 mg terbutaline (Chest 2002;122:2015-20).

The findings led the researchers to conduct a second randomized, controlled study, this time combining 3% hypertonic saline with 1.5 mg epinephrine three times a day until discharge among 27 hospitalized infants. Clinical severity scores improved significantly after 24 hours of therapy and almost a full day was shaved off the length of stay (LOS), compared with normal saline plus epinephrine in 25 infants (Chest 2003;123:481-7).

The group came back a year later with a second year of follow-up in 41 inpatients and essentially replicated their findings (Isr. Med. Assoc. J. 2006;8:169-73).

The study that caught most physicians' eyes, however, was a multicenter, double-blind Canadian trial that left the concomitant use of beta-agonists up to the discretion of the physicians who treated 96 infants hospitalized with moderately severe viral bronchiolitis (J. Pediatr. 2007;151:266-70). Even though 30% of the infants did not receive beta-agonists, the use of hypertonic saline resulted in a clinically relevant 26% reduction in LOS (from 3.5 days to 2.6 days) with normal saline. Symptoms diverged the longer the infants were treated.

Short-term improvement was not really expected, based on the theory that hypertonic saline works by rehydrating the airway surface liquid (ASL), as well as inducing cough and improving sputum mobility. The Israelis theorized that mucociliary failure, such as occurs in cystic fibrosis, also occurs in severe bronchiolitis because of dehydration of the ASL, the thin layer of fluid that covers the luminal surface of the airway.

In vitro, hypertonic saline increases airway surface thickness, decreases epithelial edema, and improves mucus rheology and transport rates. In vivo, it increases mucociliary transport in healthy subjects.

Thus, it makes sense that short-term studies have found no difference in outcomes, and that studies demonstrating positive effects on LOS and respiratory scores do so only after 24 hours of therapy. Fluid shifts take time, and cilia can only do so much.

Chinese investigators have reported similar positive outcomes, including a reduction in LOS from 7.4 to 6 days with hypertonic saline plus salbutamol in hospitalized infants (Pediatr. Int. 2010; 52:199-202). Moreover, these findings were replicated in a second study, this time using nebulized 3% hypertonic saline without concomitant bronchodilators (Clin. Microbiol. Infect. 2010 July 15 [doi:10.1111/j.1469-0691.2010.03304.x]).

We've never seen this level of consistently positive results in the data on bronchiolitis treatment in the past, and it's exciting – particularly as we have so little in our therapeutic armamentarium. It's also very interesting to have a theory of mechanism of action that meshes with the known pathology in bronchiolitis. After years of repeatedly studying beta-agonists, even though we knew that airway smooth muscle reactivity was not the major pathology, it is refreshing to see a different approach emerging. ■

DR. RALSTON *is chief of inpatient pediatrics at the University of Texas Health Science Center in San Antonio. She said she had no relevant financial disclosures.*

It is too early to say if hypertonic saline is an appropriate therapy.

BRIAN K. ALVERSON, M.D.

Much of the evidence supporting the use of nebulized hypertonic saline for acute bronchiolitis rests on changes in respiratory scores that are not likely to have clinical relevance. The true test is whether hypertonic saline can really reduce length of stay (LOS), the hard outcome that physicians and parents care about. That question remains unanswered.

No fewer than five short-term emergency department (ED) studies have failed to find a difference in outcomes between nebulized hypertonic saline and normal saline. One of those trials was by the same group of Canadian researchers that helped put nebulized hypertonic saline on the radar of many physicians (J. Pediatr. 2007;151:266-70).

When the Canadians studied hypertonic saline in the ED setting, there were no significant differences in hospital admission rates or respiratory scores after three consecutive 4-mL doses of nebulized 3% hypertonic saline in children younger than age 2 years who presented to the ED with moderately severe bronchiolitis (CJEM 2010; 12:477-84).

In addition, no large randomized trials from the United States have been conducted using our criteria for hospitalization. A recent Chinese study demonstrated a reduction in LOS with the use of hypertonic saline plus salbutamol in 93 infants hospitalized with mild to moderate bronchiolitis (Pediatr. Int. 2010;52:199-202). The reduction, however, was from 7.4 days to 6.0 days – an LOS that was more than double the U.S. average LOS of 2.5 days.

The same researchers evaluated nebulized 3% hypertonic saline without bronchodilators, and reported a similar reduction in LOS from an average of 6.4 days with normal saline to a full 4.8 days with hypertonic saline (Clin. Microbiol. Infect. 2010 July 15 [doi:10.1111/j.1469-0691.2010.03304.x]).

Dr. Susan Wu and her colleagues at Children's Hospital Los Angeles presented data, however, at the recent Pediatric Hospital Medicine 2011 meeting that contradicts these findings. Although the preliminary analysis includes subjects from only the first 2 years of the study and was not fully powered for the LOS outcome, hypertonic saline was no better than normal saline for respiratory distress, and actually resulted in a longer LOS of 3.46 days, compared with 2.74 days with normal saline (Pediatric Hospital Medicine 2011;1 [poster session B, July 29] abstract 4).

One also has to question whether the cost of respiratory therapy labor to provide such a potentially ineffective therapy can be justified in the current health care environment, when hypertonic saline hasn't been established as being superior to the guideline recommendation of supportive care only.

Some may argue that the cost of hypertonic saline is free, but a quick back-of-the-envelope calculation would suggest otherwise. If you practice in a 90-bed hospital, see 500 bronchiolitis patients per year, and have a 3-day LOS using hypertonic saline every 4 hours, that works out to 12,000 nebulizations and 400 hours of respiratory time, which ends up costing $300,000 per year. At that price tag, you could hire a full-time employee for your team.

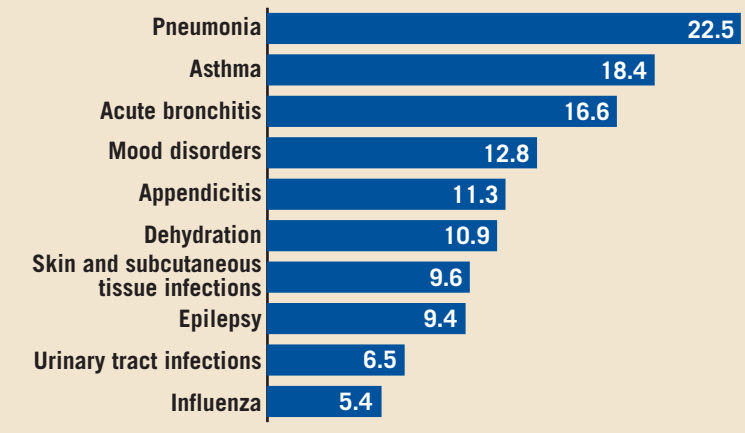
Many administrations may also insist that hypertonic saline be given with albuterol, which one could argue may in some cases actually extend LOS because of the potential for patients to desaturate.

Finally, if you're a fee-for-service hospital, there's a financial disincentive for your administration to spend $300,000 for a therapy that could actually reduce profits by shortening LOS. Hospitals adopt measures that shorten LOS, but few would be willing to implement such a strategy until a large, randomized, controlled trial conducted in the United States has proved that hypertonic saline, likely without albuterol, is both clinically and cost effective. ■

DR. ALVERSON *is director of pediatric hospital medicine at Hasbro Children's Hospital in Providence, R.I. He said that he had no relevant financial disclosures.*

DATA WATCH

Top 10 Reasons for Children's Hospital Stays, 2009*
(discharges per 10,000 population)



*Excluding newborn conditions
Source: Agency for Healthcare Research and Quality statistical brief #118 (Aug. 2011)

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Soldiers May Return With Constrictive Bronchiolitis

Common toxic exposures include open-air burn pits and desert dust storms.

BY MARY ANN MOON
Elsevier Global Medical News

Constrictive bronchiolitis should be considered in all returning veterans who report exercise limitations due to dyspnea, according to a recent report.

Lung biopsies revealed diffuse constrictive bronchiolitis in 38 of 49 previously healthy soldiers who developed unexplained exertional dyspnea and diminished exercise tolerance after serving in Iraq or Afghanistan, said Dr. Matthew S. King of the division of pulmonary and critical care medicine, Meharry Medical College, Nashville, Tenn., and his associates (N. Engl. J. Med. 2011;365:222-30).

Although most of the 38 soldiers had been exposed to smoke from a sulfur-mine fire in northern Iraq, 10 reported no potentially toxic exposures – a "particular concern" given that the potential toxic exposures among those 10 may be similar to those of most troops who were deployed to Iraq and Afghanistan.

The rare disorder is a challenge to diagnose, especially in the absence of known predisposing conditions such as rheumatologic disorders, because patients often show low-normal pulmonary function and normal radiologic results.

During a recent 5-year period, the investigators evaluated 80 soldiers from one Kentucky military base who had persistent respiratory symptoms and exercise intolerance – an extensive assessment that included a detailed review of occupational and environmental exposures. A total of 49 were referred for video-assisted thorascopic lung biopsy by their treating physicians.

Of those 49, 38 were found to have diffuse constrictive bronchiolitis. The 35 men and 3 women had a median age of 33 years (range, 23-44 years), and had served in a variety of positions. All had met the requirements of U.S. Army readiness testing wearing full combat gear before being deployed, but now became breathless after climbing a single flight of stairs.

Chest radiography had yielded normal findings in 37 of the soldiers, and high-resolution CT had done so in 25 soldiers. "Only a few soldiers had high-resolution CT showing the centrilobular nodules or expiratory air trapping that can be associated with constrictive bronchiolitis," the researchers said.

Spirometry results, lung volumes, and measures of carbon monoxide diffusing capacity had been normal in 13 of the soldiers, while another 19 had shown only isolated low carbon monoxide diffusing capacity.

During biopsy, 37 of the 38 soldiers were found to have lacy black pigment on the visceral pleural surface, and specimens showed polarizable material within the pigment consistent with inhalation of particulate matter. The biopsy specimens also showed mixed airway-wall inflammation and membranous bronchioles containing hypertrophic mural smooth muscle or fibrous thickening that narrowed the lumen in the small airways. That finding, too, is consistent with toxic inhalation.

Culturing the biopsy samples yielded negative results on all attempts to identify bacteria, fungus, or acid-fast bacilli.

Of the 38 soldiers, 28 had been exposed to smoke from a sulfur-mine fire in northern Iraq, 33 had been exposed to dust storms, 24 to incinerated solid waste in large burn pits, and 18 to incinerated human waste. However, 10 solders reported no potentially toxic exposures at all.

"This group causes particular concern, since their potential toxic exposures are shared by most personnel who were deployed to Iraq and Afghanistan," the investigators noted. "These common exposures include open-air burn pits, in which solid waste was routinely incinerated in close proximity to living quarters, and desert dust storms of such severity that they obscured visibility.

"The presenting symptoms, smoking histories, evaluations, and biopsy samples of the 10 soldiers who did not report exposure to the sulfur-mine fire were indistinguishable from those of the 28 soldiers who did report such exposure," the researchers added.

Of the 38 soldiers who responded to a 2010 follow-up survey, 19 had left the military with a "disabled" rating, while 8 were still serving "despite their inability to complete a 2-mile run within the regulation time"; 22 said their respiratory problems limited their job opportunities.

The study was supported in part by the National Center for Research Resources. One coauthor reported ties to Actelion Pharmaceuticals. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: These young soldiers presented with alarming symptoms – shortness of breath after climbing a single flight of stairs. Most had a documented inhalational insult, but this was not universal. While basic investigations were not revealing, cardiopulmonary exercise testing did document significant limitation compared with a military control group. As mentioned by the authors, the diagnosis of constrictive bronchiolitis is frequently difficult – lung biopsy is required and was diagnostic in these instances. Our understanding of the consequences of various battlefield exposures is growing. Concerns about potential longer-term consequences may also be justified, as it is possible that an inhaled insult could cause disease many years in the future. We still have much more to learn and observe; in the meantime, it would be judicious for the clinician to thoroughly investigate individuals returning from the field with any respiratory complaints.

Paraesophageal Hernia Repair Can Boost Lung Function

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS – Improvements in pulmonary function tests and subjective complaints of breathlessness appear to be underappreciated benefits of the surgical repair of giant paraesophageal hernias.

Symptom assessment of these patients has generally focused on reflux and dysphagia, but these hernias also adversely affect pulmonary function. Repair most benefits patients who are older, have bigger hernias, and have worse baseline pulmonary function, said Dr. Philip W. Carrott Jr., of Virginia Mason Medical Center, Seattle.

"Patients with giant paraesophageal hernia and coexistent dyspnea or positional breathlessness should be reviewed by an experienced surgeon for elective repair, even when pulmonary comorbidities exist," Dr. Carrott said at the annual meeting of the Western Thoracic Surgical Association.

He based this advice on a single-center, retrospective, cohort study involving 120 patients who had pulmonary function tests preoperatively and again at a median of 106 days after surgery.

The overall group averaged 10% increases over baseline (*P* less than .001) in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), vital capacity, and volume-adjusted mid-expiratory flow (IsoFEF25-75), as well as a 2.9% increase in the diffusing capacity of the lung (DLCO).

The larger a patient's hernia as expressed by percent intrathoracic stomach (ITS) on preoperative contrast studies, the greater the improvement in pulmonary function tests after surgery. Indeed, hernia size was the strongest predictor of improvement. For example, FVC improved by an average of 4.7%, compared with reference values, in patients with the smallest hernias as expressed in a percent ITS of less than 50%, as compared with a 6.0% gain in patients with a preoperative 50%-74% ITS, a 9.1% improvement in those with 75%-99% ITS, and a 14.9% gain in FVC in patients with 100% ITS.

The postoperative improvement in lung function increased with each decade of patient age.

Patients with the worst preoperative lung function tended to have the biggest hernias – and the greatest objective and subjective improvements after surgery. For example, 36% of subjects had a reduced baseline FEV_1 not more than 75% of the reference value. Their vital capacity improved by 0.45 L, as compared with 0.23 L in patients without a reduced baseline FEV_1. And their DLCO improved by 1.23 mL CO/min per mm Hg, compared with just 0.23 in patients whose baseline FEV_1 was more than 75% of the reference value.

Of 63 patients who reported preoperative dyspnea, 47 (75%) noted subjective improvement in their respiratory function after hernia repair. Intriguingly, so did 30 of 57 patients (53%) not complaining of dyspnea at baseline.

Study participants averaged 74 years of age, with a median of four preoperative symptoms. The most common were heartburn in 59%, early satiety in 54%, dyspnea in 52%, dysphagia in 47%, chest pain in 40%, and regurgitation in 39%.

An open Hill repair with no hiatal reinforcement was performed in 99% of patients, and 97% of the operations were elective. ■

COMMENTARY

Dr. Richard Fischel, FCCP, comments: Despite this study's retrospective nature and moderate sample size, the data reinforce what many surgeons have been noting anecdotally for years. The fact that the largest improvement was seen in the sickest patients coincides with other studies of respiratory function such as the national emphysema treatment trial or NETT, which addressed a larger population in a prospective study. In this study, all cases were done with an open surgical technique and one can only wonder if the results may have been even better had a laparoscopic approach been utilized. This study can be useful to surgeons discussing elective repair of paraesophageal hernia with their patients, especially those with impaired respiratory function, while being cautious to avoid any "promise" of improved lung function.

Crizotinib Approval Advances Personalized Lung Ca Tx

BY MIRIAM E. TUCKER
Elsevier Global Medical News

The swift approval of crizotinib capsules by the Food and Drug Administration as the first and only targeted therapy for locally advanced or metastatic ALK-positive non–small cell lung cancer represents another milestone in biomarker-driven, personalized medicine.

Crizotinib was approved, along with a companion diagnostic test, Abbott Molecular's Vysis ALK Break Apart FISH Probe Kit, which identifies the anaplastic lymphoma kinase (ALK) fusion gene that the drug targets. Pfizer is authorized to market crizotinib as Xalkori for use in patients who test positive for the abnormality.

The ALK fusion gene – comprising portions of the EML4 (echinoderm microtubule–associated proteinlike 4) gene and the ALK gene – is present in about 3%-5% of all patients with NSCLC. Although the percentage is small, it translates to approximately 6,000-11,000 new patients annually in the United States.

"Having this number of people we can affect is really an important development in oncology," commented Dr. Mark G. Kris, FCCP, chief of the thoracic oncology service at Memorial Sloan-Kettering Cancer Center in New York, during a press briefing sponsored by Pfizer. The approval "is a delivery on the promise of personalized medicine and genomic medicine," said Dr. Kris, a professor of medicine at Cornell University in New York.

The experimental BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trials program at the University of Texas M.D. Anderson Cancer Center in Houston has shown that it is feasible to biopsy late-stage NSCLC patients and base the choice of therapies on the results of molecular tests for abnormal KRAS, EGFR, and other genes.

Currently, the Lung Cancer Mutation Consortium is engaged in a collaborative project profiling 10 genes, including KRAS, ALK, and EGFR, in 1,000 patients at participating cancer centers. Investigators have reported that 280 (54%) of the first 516 patients were found to have at least one known driver mutation.

In clinical trials, crizotinib benefited nearly all patients with the ALK fusion gene, although the degree of benefit varied, Dr. Kris said. And withholding crizotinib from patients who test negative means they will be spared the side effects and the waste of time and resources associated with a treatment that won't work for them.

The FDA approval was based on two multicenter, single-arm studies that enrolled 255 late-stage NSCLC patients who tested positive for the ALK fusion gene. Most patients had prior chemotherapy. Objective response rates were 50% (median duration, 42 weeks) in one study and 61% (median duration, 48 weeks) in the other.

The FDA warned that crizotinib has been associated with potentially life-threatening pneumonitis (4 of 255 patients; 1.6%); the drug should be stopped permanently in patients with treatment-related pneumonitis, the agency said. Pregnancy is also a contraindication.

Crizotinib was considered under the FDA's priority review program for drugs with the potential to provide major advances in diseases for which no effective therapy exists. Confirmatory trials are required.

Pfizer is already conducting two randomized, open-label, postmarketing phase III studies: one comparing the safety and efficacy of crizotinib with standard of care chemotherapy (pemetrexed or docetaxel) in patients with previously treated, advanced, ALK-positive NSCLC, and the other comparing efficacy and safety of the agent to pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with advanced, ALK-positive, nonsquamous NSCLC, according to a Pfizer statement.

Recommended dosing is 250 mg taken orally twice daily. In some patients, a dosing interruption and/or dose reduction to 200 mg taken orally twice daily may be required; if further reduction is necessary, the label recommends 250 mg taken orally once daily.

Monthly treatment with crizotinib will cost $9,600. Because the tumor is driven by the mutation, the treatment is indefinite. Several patients from the trials have now been taking the drug for more than a year.

Pfizer has two financial assistance programs for patients. Information about eligibility can be obtained by calling First Resource (877-744-5675) or by visiting www.xalokori.com.

Dr. Kris is a consultant for Pfizer. ■

Targeted Tx Improving Outcomes

Lung Cancer • *from page 1*

at Harvard Medical School and the Dana Farber Cancer Institute, both in Boston, takes credit for starting both; his EGFR program began 7 years ago and KRAS testing has been going for 5 years, he said.

Today, testing at several major U.S. cancer centers has added investigational tests for genes such as HER2, PIK3CA, ALK, MET, MEK, BRAF, AKTI, and NRAS. The Lung Cancer Mutation Consortium is in the midst of profiling 10 genes in 1,000 patients.

"Progress has been so dramatic. All but EGFR and KRAS came in the past year," said Marileila Varella Garcia, Ph.D., professor of medical oncology at the University of Colorado in Denver and a leader of the consortium. "At the University of Colorado, it took us 18 months to optimize the test, but now we ... test for 10 mutations for the same cost as testing for one."

At the Yale Cancer Center, the routine profiling list stands at 13 genes, said Dr. Roy S. Herbst, chief of medical oncology at Yale in New Haven, Conn. "Right now, the only test that [insurers] pay for is the EGFR mutation test. Once the ALK story is more validated, they will probably pay to find ALK translocations, but with a chip, for the same money you can also test for other mutations for research," Dr. Herbst said. "In the United States, testing for EGFR mutations is standard of care at most top cancer centers. EGFR is an actionable mutation, with patients considered for erlotinib treatment."

Dr. Varella Garcia, Dr. Johnson, and their collaborators from the consortium reported on the first 516 patients with advanced lung cancer who were tested with the 10-gene panel. The results showed that 280 of the tumors (54%) carried at least one mutation in at least one of the 10 genes that the consortium tested.

'It was surprising that they found actionable mutations in more than half of the tumors they have tested so far.'

DR. GANDARA

KRAS mutations were most prevalent, in 22% of the patients, followed by EGFR mutations in 17%, ALK rearrangement in 10%, MET amplifications in 4%, and a smaller number of genetic changes in each of the other six genes tested. Most mutations were mutually exclusive, with only 3% of tumors having mutations in two genes, and no tumors with mutations in three or more genes.

"It was surprising that they found actionable mutations in more than half of the tumors they have tested so far. That is very promising," Dr. Gandara said.

Over the next 3-4 years, further studies will likely validate additional genes and mutations, perhaps encompassing about 90% of patients with advanced-stage lung cancer by 2015, Dr. Varella Garcia said in an interview. It's also likely that a small percentage of these cancers won't link with any single, identifiable gene mutation and will instead depend on changes in several pathways, something much harder to sort out.

The number of "actionable" gene mutations (mutations that, once found, can receive a targeted treatment) also remains limited but growing. Until recently, the list had a single gene, EGFR. Patients with EGFR mutations are candidates for treatment with erlotinib (Tarceva) or gefitinib (Iressa, which was not approved for routine U.S. use), both drugs from the tyrosine kinase inhibitor class.

A second, recent success story for targeted treatment involves the ALK fusion mutation, a genetic profile of tumors responsive to crizotinib (see story above).

This year's meeting featured three main themes for patient management, but ultimately all three boil down to molecular biomarkers and molecularly directed treatment, Dr. Gandara said. One main theme – histologic profiles of advanced lung cancer – has been an important focus, but "histology is a transient selection method," he said. "At best, histology is a crude molecular selection device" superseded by molecular profiling itself.

Another important, recent focus has been maintenance therapy, but "the real questions are who gets further treatment after platinum-based induction, and when should they get it," questions best answerable by molecular profiling, he added.

"We have many 'druggable' molecular targets," Dr. Gandara noted.

"For almost every mutation [of the 10 genes that] the consortium is testing, we have phase I treatment trials underway," said Dr. Varella Garcia. Patients with tumors that carry KRAS and MEK mutations receive an investigational MEK inhibitor. Patients with tumors that contain HER2 mutations receive trastuzumab (Herceptin) as an investigational agent. Patients with MET mutations receive a MET monoclonal antibody.

Despite success so far, and pervasive optimism that current studies will validate new treatments, researchers cautioned that management of advanced lung cancer also has some unavoidable limitations.

"We will never cure advanced lung cancer; we can make it a chronic disease," Dr. Varella Garcia said. Effective treatment means that patients' quality of life improves, and their disease comes under control for several years. But "it is almost universal that these patients will eventually progress again. We cannot cure advanced lung cancer. We can control it with new, targeted treatments that use oral drugs with low toxicity."

Dr. Gandara, Dr. Johnson, and Dr. Herbst disclosed relationships with numerous pharmaceutical and biotechnology companies. Among these, Dr. Johnson listed stock in Celgene and a patent for EGFR testing by Genzyme. Dr. Varella Garcia said that she has been a consultant to Abbott. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: These are exciting times for those with an interest in lung cancer. Major new discoveries seem to appear every month when the journals come out. This article discusses several of the recent advances. Personally, I came away from this article with four key phrases: "culture change for the field," "ungrouping of NSCLC," "actionable mutations," and "druggable molecular targets." Once you understand the context, you may wish to add these phrases to your personal lung cancer lexicon.

USAGE

- **To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO® and other antibacterial drugs, TEFLARO should be used to treat only CABP or ABSSSI that are proven or strongly suspected to be caused by susceptible bacteria.**
- **When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.**

INDICATIONS

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- TEFLARO is also indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

IMPORTANT SAFETY INFORMATION

Contraindications

- TEFLARO is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

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

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

INDICATIONS AND USAGE

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
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- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity Reactions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with TEFLARO is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.
- If an allergic reaction to TEFLARO occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

Clostridium difficile-associated Diarrhea

- *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including TEFLARO, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible.

Broad-spectrum coverage for treating CABP and ABSSSI

Bactericidal Activity Against a Broad Spectrum of Gram-positive and Gram-negative Pathogens, Including *S. pneumoniae* in CABP and MRSA in ABSSSI[1]

Proven efficacy in 2 common infections
in patients admitted to the hospital[1,2]

CABP | **ABSSSI**

- **Convenient q12h dosing in CABP and ABSSSI[1]**
  - **600 mg intravenous over 1 hour**
  - **Treatment duration**
    - **5-7 days for CABP**
    - **5-14 days for ABSSSI**

IMPORTANT SAFETY INFORMATION

Direct Coombs' Test Seroconversion

- Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving TEFLARO and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with TEFLARO, drug-induced hemolytic anemia should be considered. If drug-induced hemolytic anemia is suspected, discontinuation of TEFLARO should be considered and supportive care should be administered to the patient if clinically indicated.

Development of Drug-Resistant Bacteria

- Prescribing TEFLARO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in CABP

TEFLARO CABP Study Designs[1,3]

Type of trial: Two randomized, multicenter, multinational, double-blind, noninferiority trials

Study population: 1231 adults with a diagnosis of CABP

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-7 days;
Ceftriaxone – 1 g ceftriaxone administered IV over 30 minutes every 24 hours for 5-7 days

Adjunctive therapy: CABP Trial 1, two doses on Day 1 of oral clarithromycin 500 mg every 12 hours;
CABP Trial 2, no adjunctive macrolide therapy

TEFLARO Study Populations

Day 4 Population (mITT)*		A microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline.
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
MITTE	Modified Intent-to-treat Efficacy	All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.
CE	Clinically Evaluable	All subjects in the MITTE population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the patient's outcome.
ME	Microbiologically Evaluable	All subjects in the CE population who had at least one typical bacterial pathogen identified at baseline from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid).

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to both (a) be in stable condition according to consensus treatment guidelines, and (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms.

† The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary MITTE and CE populations and clinical cure rates at TOC by pathogen in the ME population.

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only CABP that is proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

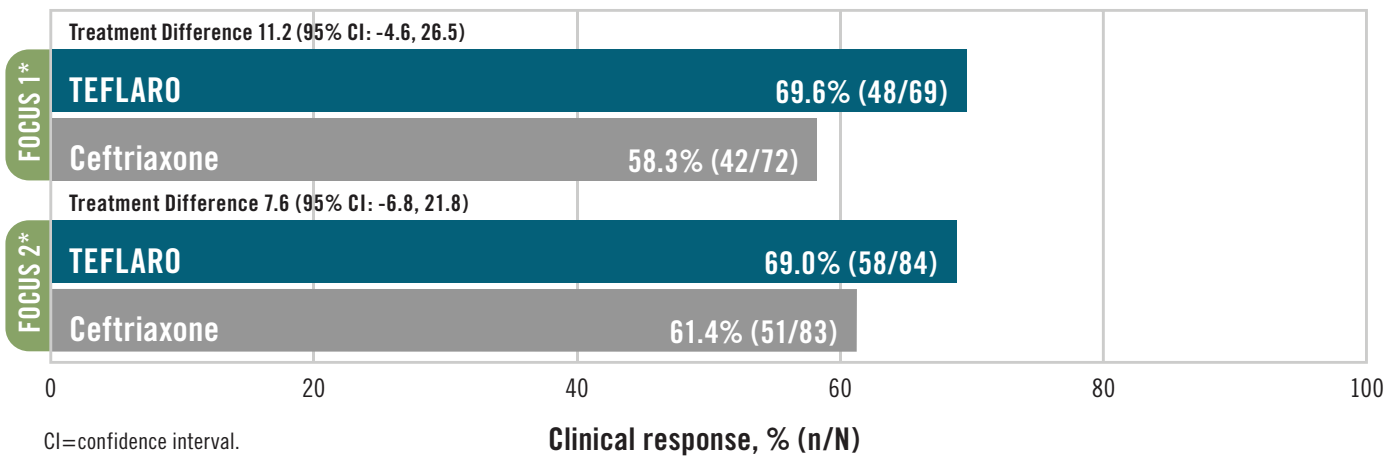
Adverse Reactions

- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the TEFLARO group and 0.5% in the comparator group.
- No adverse reactions occurred in greater than 5% of patients receiving TEFLARO. The most common adverse reactions occurring in >2% of patients receiving TEFLARO in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

CABP

TEFLARO Demonstrated Clinical Response at Day 4 (mITT) in Community-Acquired Bacterial Pneumonia[1]

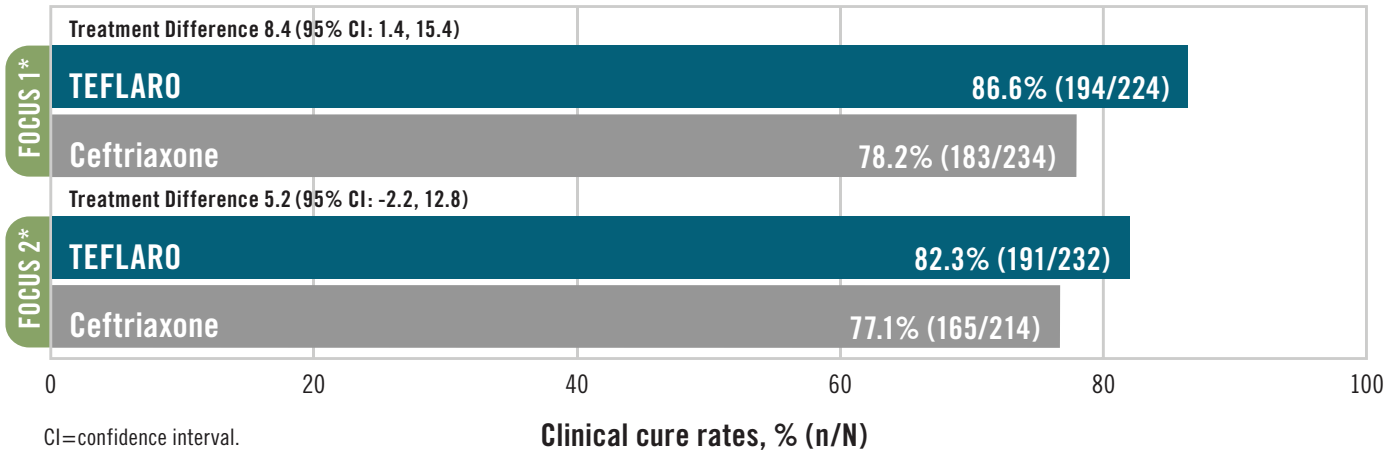


CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

CABP

TEFLARO Demonstrated Efficacy at TOC† (CE) in Community-Acquired Bacterial Pneumonia[1]



CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

Patients with known or suspected MRSA were excluded from both trials.

*FOCUS=Ce**f**tar**o**line **C**ommunity-Acquired Pne**u**monia Trial v**s** Ceftriaxone in Hospital Patients. FOCUS 1=CABP Trial 1, FOCUS 2=CABP Trial 2.

†There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish noninferiority.

IMPORTANT SAFETY INFORMATION

Drug Interactions

- No clinical drug-drug interaction studies have been conducted with TEFLARO. There is minimal potential for drug-drug interactions between TEFLARO and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.

Teflaro®
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Demonstrated efficacy in ABSSSI

TEFLARO ABSSSI Study Design[1,3]

Type of trial: Two identical, randomized, multicenter, multinational, double-blind, noninferiority trials

Study population: 1396 adults with clinically documented complicated skin and skin structure infection

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-14 days;
Vancomycin plus aztreonam – 1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours for 5-14 days

Treatment duration: Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed

TEFLARO Study Populations

Day 3 Population*		The analysis evaluated patients with lesion size ≥75 cm^2 and having one of the following infection types: – Major abscess with ≥5 cm of surrounding erythema – Wound infection – Deep/extensive cellulitis
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
CE	Clinically Evaluable	Patients in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal clinical disease criteria for cSSSI and all evaluability criteria, including subjects who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for which sufficient information regarding the cSSSI site is available to determine the subject's outcome, and for which there were no confounding factors that interfered with the assessment of that outcome.
ME	Microbiologically Evaluable	This population consists of a subset of subjects from the CE population who had at least one bacterial pathogen identified from a blood culture or culture of an adequate microbiological sample obtained from the cSSSI site at baseline and who had susceptibility testing performed on at least one of the isolated baseline pathogens.

*To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep/extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3.

†The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary CE and MITT populations and clinical cure rates at TOC by pathogen in the ME population.

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI that is proven or strongly suspected to be caused by susceptible bacteria.

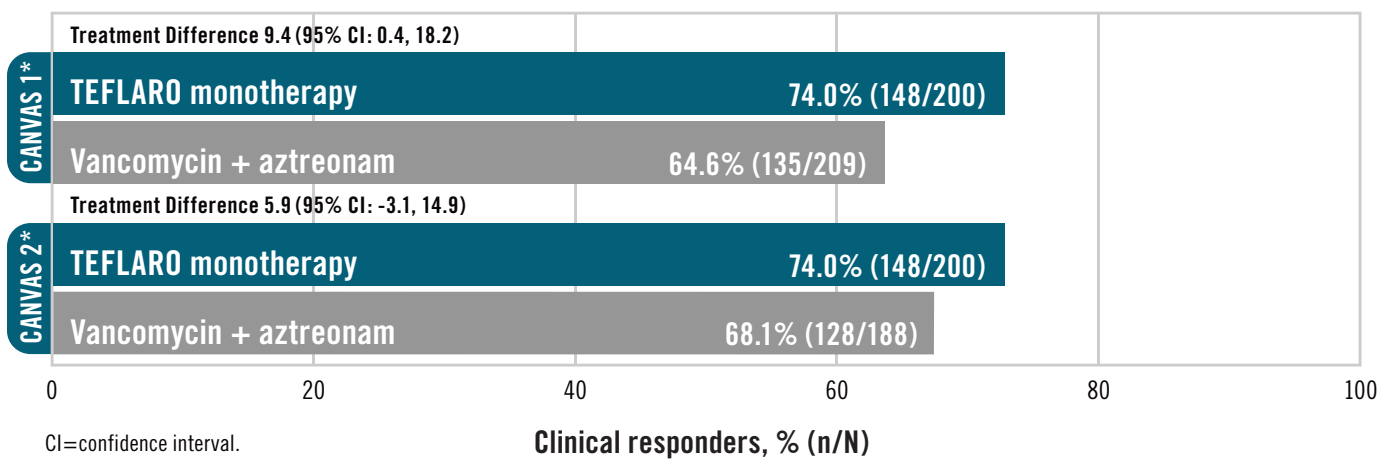
IMPORTANT SAFETY INFORMATION

Use in Specific Populations

- TEFLARO has not been studied in pregnant women. Therefore, TEFLARO should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
- It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEFLARO is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Because elderly patients, those ≥65 years of age, are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should therefore be based on renal function.
- Dosage adjustment is required in patients with moderate (CrCl >30 to ≤50 mL/min) or severe (CrCl ≥15 to ≤30 mL/min) renal impairment and in patients with end-stage renal disease (CrCl <15 mL/min).
- The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.

ABSSSI

TEFLARO Demonstrated Clinical Response at Day 3 in Acute Bacterial Skin and Skin Structure Infections[1]

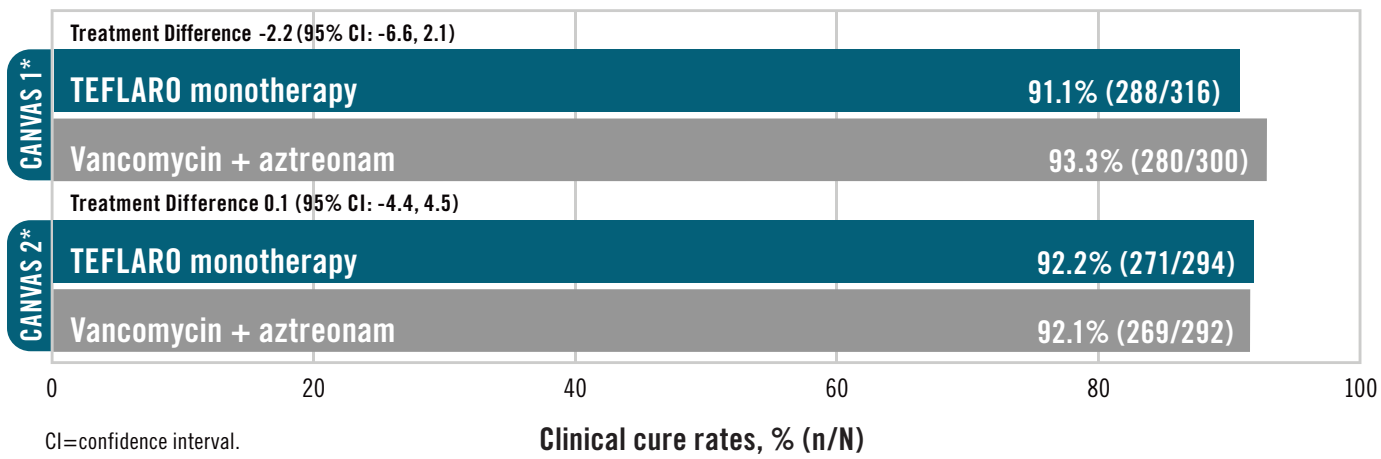


CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

ABSSSI

TEFLARO Demonstrated Efficacy at TOC† (CE) in Acute Bacterial Skin and Skin Structure Infections[1]



CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

*CANVAS=**C**eft**a**rolin**e** **v**s V**a**ncomycin in **S**kin and Skin Structure Infection. CANVAS 1=ABSSSI Trial 1, CANVAS 2=ABSSSI Trial 2.

† There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to vancomycin plus aztreonam based on clinical response rates at TOC cannot be utilized to establish noninferiority.

Please see brief summary of Prescribing Information on following page.
Please also see full Prescribing Information at www.TEFLARO.com.

References: 1. TEFLARO (ceftaroline fosamil) [prescribing information]. St Louis, MO: Forest Pharmaceuticals, Inc; 2011. **2.** Elixhauser A, Owens P. *Reasons for being admitted to the hospital through the emergency department, 2003.* Healthcare Cost and Utilization Project Statistical Brief #2. February 2006. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/reports/statbriefs/sb2.pdf. Accessed February 10, 2011. **3.** Data on file. Forest Laboratories, Inc.

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Delayed Parenteral Nutrition Better in Critically Ill

BY MARY ANN MOON
Elsevier Global Medical News

In critically ill adults who cannot be adequately fed enterally, withholding parenteral nutrition until day 8 is a superior strategy to initiating it on day 2.

In a study directly comparing the two approaches, rates of ICU, in-hospital, and 90-day mortality were similar between "early" and "late" parenteral nutrition, as were nutrition-related complications. However, the late approach yielded a higher rate of discharge from the ICU within 8 days, a shorter median ICU stay, a shorter hospital stay without any decrease in functional status, a shorter duration of mechanical ventilation, a shorter course of renal-replacement therapy, a lower rate of liver enzyme abnormalities, and lower health care costs.

"Our results do not support the conclusions from previous observational studies that earlier achievement of nutritional targets improves the outcome for critically ill patients," said Dr. Michael P. Casaer of the department of intensive care medicine at the University Hospitals of the Catholic University of Leuven (Belgium), and his associates.

Nutritional deficits predispose ICU patients to muscle wasting, weakness, and delayed recovery. Currently, clinical practice guidelines in Europe recommend that clinicians consider initiating parenteral nutrition within 2 days of ICU admission if the enteral route cannot provide adequate nutrition. In contrast, guidelines in the United States and Canada recommend early enteral nutrition "but suggest that parenteral nutrition not be initiated concomitantly, thus advising that hypocaloric nutrition be tolerated during the first week," the investigators said.

They compared patient outcomes between early and late parenteral nutrition in a prospective randomized trial involving 4,640 adults admitted to seven Belgian ICUs. The study subjects were stratified according to 16 diagnostic categories to control for the potentially confounding effect of illness severity on outcomes.

The primary efficacy end point – the proportion of patients discharged alive from the ICU within 8 days – was higher with late parenteral nutrition, despite the fact that more patients in this group developed hypoglycemia during their stay, the investigators said (N. Engl. J. Med. 2011;365:506-17).

The median ICU stay was 1 day shorter with late parenteral nutrition, and the median hospital stay was 2 days shorter. Yet functional status at hospital discharge, as measured by both the 6-minute walk distance and performance of the activities of daily living, was comparable between the two groups.

Subgroup analyses showed that these findings were consistent regardless of patients' body mass index, degree of estimated nutritional risk, and presence or absence of sepsis at baseline.

The study results suggest that "withholding macronutrients in the early stages of a critical illness, regardless of the route of nutrition, may enhance recovery.

This study was supported by the Methusalem program of the Flemish government, the Catholic University of Leuven, the Research Foundation of Flanders, University Hospitals Leuven, and an unrestricted grant from Baxter Healthcare. No conflicts of interest were reported. ■

COMMENTARY

Dr. Carl A. Kaplan, FCCP, comments: Depending on the institution in which one practices, there may be significant emphasis on use of parenteral nutrition early with the presumption that it will improve outcomes.

This study demonstrated the opposite: that with delayed initiation of parental nutrition (after day 8), there were reductions in ICU length of stay, hospital LOS, days on ventilator, days on renal replacement, infection rate, and costs. And, importantly, with delayed initiation of parental nutrition, there was no decrease in functional status at time of hospital discharge.

Chest Physicians Urged to Capitalize on P4P

BY SUSAN LONDON
Elsevier Global Medical News

DENVER – "I encourage you to think of pay for performance as an opportunity, not a threat," Dr. Jeremy M. Kahn advised attendees of an international conference of the American Thoracic Society. "View this as an opportunity to partner with payers [and] to provide higher-quality care, not as a threat to autonomy and independence."

The society recently took up the issue of pay for performance (P4P, also known as value-based purchasing) in a policy statement that addressed the potential implications of this health care financing mechanism for pulmonary, critical care, and sleep medicine (Am. J. Respir. Crit. Care Med. 2010;181:752-61).

"There are dual crises facing health care," commented Dr. Kahn of the University of Pittsburgh. "Not only do we spend too much, but we don't get enough" quality in terms of population coverage with recommended care. A major driver is the current approach to financing health care, which rewards quantity and efficiency.

"Value-based purchasing turns that on its head and says we shouldn't be incentivizing quantity, nor should we be incentivizing efficiency alone. But we should explicitly be incentivizing quality," he explained.

To be sure, the P4P concept has some limitations, such as the difficulty of defining and measuring quality, and the fact that some outcomes, such as certain adverse events, are largely beyond physicians' control, Dr. Kahn acknowledged.

Investigators recently assessed whether P4P works in a systematic review of 128 studies (BMC Health Serv. Res. 2010;10:247). "This systematic review is notable because every conceivable outcome was represented in these studies: P4P improves health care, P4P worsens health care, P4P does nothing for health care," he commented. "If anything, what we can take away from this systematic review is not that P4P is useless, but [when] we construct a P4P program, we need to be very careful about how we design it."

Indeed, P4P could have unintended consequences. For example, it might improve documentation of care instead of actual quality of care; reward physicians who are already high performers without increasing quality; encourage misuse or overuse of care; lead to dumping (getting rid of high-risk patients) or cream skimming (seeing only low-risk patients), which could accentuate racial disparities in care; and punish poorly resourced providers, such as those in safety net hospitals. It might also worsen aspects of care that are not measured. "If I'm being incentivized to do three things, I'm going to do those three things really well, and may not also do the other things," Dr. Kahn explained.

But there are also several ways to proactively circumvent these pitfalls. They include varying measures and rotating measures to encourage people to think about the gamut of quality, and rewarding not only success, but improvement as well. Also, planners could "specifically design these programs to target at-risk populations, recognizing explicitly that P4P could create disparities, and design programs specifically to eliminate health care disparities," he said. "I think if we design these programs in these four ways, we actually can achieve more benefit than harm."

Several local and health plan P4P programs are already ongoing. And as of October 2008, Medicare began declining to pay for so-called never events, largely preventable hospital-acquired conditions such as DVT and advanced pressure ulcers.

This system will be broadened in a few ways, according to Dr. Kahn. First, the new Patient Protection and Affordable Care Act will reinforce the previous Medicare commitment to P4P. Second, the current pay-for-reporting system for hospitals (www.HospitalCompare.hhs.gov) will be transitioned to P4P systems for both hospitals and physicians.

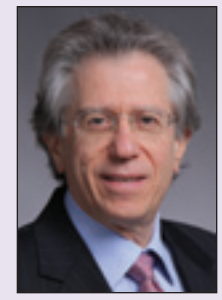
Inpatient value-based purchasing will be initiated in October 2012, with a 1% across-the-board reimbursement cut, a combination of process, outcome, and satisfaction measures into a single performance score, and payment based on performance score, he explained.

Also in the near future, the Physician Quality Reporting System, currently a pay-for-reporting system as well, will become a P4P system. "Get to know this system, because if you don't understand it now, you're going to need to later," he advised.

"P4P is a quite innovative and likely necessary approach to improving quality," concluded Dr. Kahn. "We have to think that *not* implementing P4P is accepting that we have the best payment system, which is clearly not working."

Dr. Kahn disclosed receiving in-kind research support from Cerner. ■

COMMENTARY



Dr. Stuart Garay, FCCP, comments: Pay-for-performance programs are firmly entrenched for both private insurers and Medicare. While the evidence base for their effectiveness is still a work in progress, pay for performance (P4P) is here to stay. The first wave of P4P programs focused on "process" (i.e., requiring doctors to follow certain protocols, such as measuring a PEFR for asthmatics or a hemoglobin A_{1c} in diabetics). However, following certain processes does not guarantee good results. As P4P evolves, the focus will be on outcomes and results. Dr. Jeremy Kahn asserts that we should incentivize quality, not quantity or efficiency. However, that may be easier said than done. A big question is how quality is defined. Furthermore, certain adverse events are beyond a physician's control. Nonetheless, the new Patient Protection and Affordable Care Act reinforces Medicare's commitment to P4P with an emphasis on outcomes. Although the patient plays a role, the major onus will be on physicians. The "P4P train has pulled out of the station," and we physicians better be on board to help steer its course.

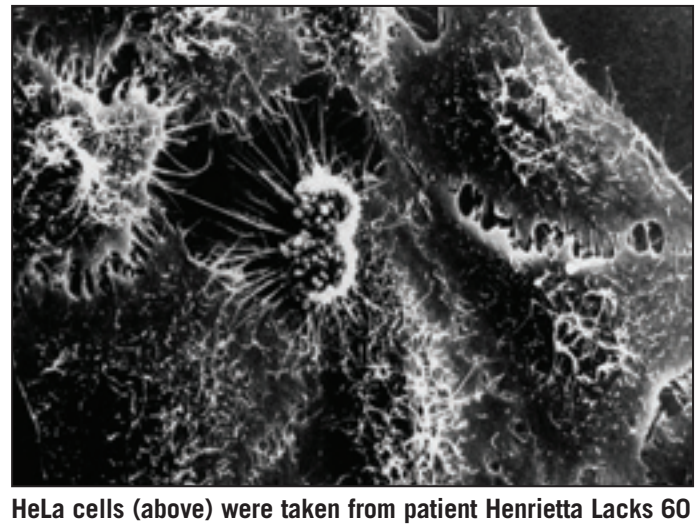
HHS Plans Revamp of Human Research Rules

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

The federal government plans to overhaul the rules for conducting research with human subjects with the aim of bringing the regulations in line with the realities of research in the 21st century.

The possible changes range from relying on a single institutional review board for multicenter studies to simplifying informed consent forms. This is the first time the regulations on human subjects' research, known as the Common Rule, have been updated since 1991.

While the Common Rule was a landmark development in the protection of research participants, those rules were developed during a "simpler time," Dr. Howard Koh, assistant secretary for health at HHS, said during a briefing with reporters. Twenty years later, human subjects' research includes a variety of new areas such as genomics and behavioral and social science research, as well as studies utilizing the Internet and large-scale data networks. "These changes in the research landscape have raised questions regarding the effectiveness of the current regulatory framework," he said.



COURTESY NATIONAL CANCER INSTITUTE

HeLa cells (above) were taken from patient Henrietta Lacks 60 years ago, before informed consent was required for research.

With that in mind, HHS is proposing to offer greater protection to study participants in several ways, such as:

► Giving participants the right to say whether researchers can use their biospecimens in future research.

► Helping researchers to craft informed consent forms that are easier to understand.

► Making data security and information protections uniform across all studies that involve potentially identifiable patient information.

► Developing a more systematic approach to collecting adverse event data from ongoing studies.

Officials also aim to ease regulatory burdens for researchers in the following ways:

► Designing review requirements to match the risk posed to research subjects.

► Ensuring that any guidance issued by the federal government is consistent across departments.

► Allowing research at multiple sites to be overseen by a single institutional review board.

HHS also seeks to expand the reach of the regulation by extending it to all studies conducted by institutions that receive federal funding for human subjects research from a Common Rule agency.

The proposal is being well received in the research community. Mary Woolley, president and CEO of Research!America, a not-for-profit organization that advocates for public and private funding of medical research, said the proposal would benefit both patients and researchers because it streamlines some of the process while adding patient protections.

Holly A. Taylor, Ph.D., of the Berman Institute of Bioethics at the Johns Hopkins University, Baltimore, praised the regulation's focus on improving the informed consent process.

Dr. Taylor, who has conducted her own research on informed consent, said she agrees with HHS that, in many cases, the forms have become too long and complex for patients to understand. She urged the agency to work with investigators, who aren't trained to write for a consumer audience, on rewriting the forms. It will be important for the government to tell investigators not just what to include in the form but how to do it, she said. "Given where we started, having a form like this was a really great idea. But there are ways now that it is sort of defeating its own purpose," she said. ■

Important safety information

Because of the risks of liver injury and birth defects, Tracleer may be prescribed and dispensed only through the Tracleer Access Program (T.A.P.), a restricted distribution program, by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

Liver injury

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should be obtained.

Contraindications

Tracleer is contraindicated with cyclosporine A, glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

Warnings and precautions

In clinical trials, Tracleer caused ALT/AST elevations (>3 × ULN) in 11% of patients accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 × ULN.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

Preclinical data and an open-label safety study (N=25) showed a decline in sperm count of ≥50% in 25% of Tracleer-treated patients after 3 or 6 months. After 6 months, sperm count remained in normal range, with no changes in sperm morphology or motility, or hormone levels. Endothelin receptor antagonists such as Tracleer may adversely affect spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

If signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. Tracleer should be discontinued.

Adverse events

In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo (≥2%) were respiratory tract infection, edema, hypotension, sinusitis, arthralgia, liver function test abnormal, palpitations, and anemia.

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Indication

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Please see accompanying brief summary of prescribing information, including ***BOXED WARNING*** *about liver injury and pregnancy, on following pages.*

*Patients ineligible for the Tracleer Patient Coupon Program include any patients whose prescriptions are paid for by the government, Medicare, Medicaid, VA/DOD (Tricare), or Indian Health Service, patients in Massachusetts and Puerto Rico, or where prohibited by law.

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WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. [see **Warnings and Precautions**].

Liver Injury

In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly [see **Dosage and Administration, Warnings and Precautions**]. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction [see **Dosage and Administration**].

Elevations in aminotransferases require close attention [see **Dosage and Administration**]. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Teratogenicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data [see **Contraindications**]. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer [see **Drug Interactions**]. Monthly pregnancy tests should be obtained.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

Considerations for use

Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.

Required Monitoring

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

Dosage Adjustments for Patients Developing Aminotransferase Elevations

The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations >3 x ULN

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.

If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

Use in Females of Childbearing Potential

Initiate treatment in females of child-bearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUS inserted do not require other forms of contraception. Effective contraception must be practiced throughout treatment and for one month after stopping Tracleer. Females should seek contraceptive advice as needed from a gynecologist or similar expert. Urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer [see **Boxed Warning, Contraindications, Drug Interactions**].

Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function [see **Warnings and Precautions**].

Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg twice daily. There is limited information about the safety and efficacy of Tracleer in children between the ages of 12 and 18 years.

Use with Ritonavir

Co-administration of Tracleer in Patients on Ritonavir

In patients who have been receiving ritonavir for at least 10 days, start Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see **Drug Interactions**].

Co-administration of Ritonavir in Patients on Tracleer

Discontinue use of Tracleer at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see **Dosage and Administration** and **Drug Interactions**].

Treatment Discontinuation

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

DOSAGE FORMS AND STRENGTHS

Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration.

62.5 mg tablets: film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62,5"

125 mg tablets: film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125"

CONTRAINDICATIONS

Pregnancy Category X *[see BOXED WARNING]*

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and large blood vessels. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of child bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should also be obtained. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. [see **Use in Specific Populations**].

Use with Cyclosporine A

Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated [see **Drug Interactions**].

Use with Glyburide

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore co-administration of glyburide and Tracleer is contraindicated [see **Drug Interactions**].

Hypersensitivity

Tracleer is contraindicated in patients who are hypersensitive to bosentan or any component of the product. Observed reactions include rash and angioedema [see **Adverse Reactions**].

WARNINGS AND PRECAUTIONS

Potential Liver Injury

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury.

Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances [see **Dosage and Administration**].

Patients with Pre-existing Hepatic Impairment

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration**]. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult [see **Boxed Warning**].

Fluid Retention

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients [see **Clinical Studies**].

In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer therapy.

Decreased Sperm Counts

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

Should signs of pulmonary edema occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer

Because of the risks of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P. can be obtained by calling 1-866-228-3546.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P. and renew patients' enrollment annually thereafter.
- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.
- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

Potential liver injury [see **Boxed Warning, Warnings and Precautions**]

Fluid retention [see **Warnings and Precautions**]

Clinical Studies Experience

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N=94 for 1 year; N=61 for 1.5 years and N=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N=328) to bosentan ranged from 1 day to 1.7 years (N=174 more than 6 months and N=28 more than 12 months).

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

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on bosentan was abnormal liver function.

The adverse drug events that occurred in ≥3% of the bosentan-treated patients and were more common on bosentan in placebo-

controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

Adverse events* occurring in ≥3% of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan N=258		Placebo N=172	
	No.	%	No.	%
Respiratory Tract Infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest Pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Liver Function Test Abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	–	

*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

Combined data from Study-351, BREATHE-1 and EARLY

Postmarketing Experience

There have been several post-marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the post approval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

- Unexplained hepatic cirrhosis [see **Boxed Warning**]
- Liver failure [see **Boxed Warning**]
- Hypersensitivity [see **Contraindications**]
- Thrombocytopenia
- Rash
- Jaundice
- Anemia requiring transfusion
- Neutropenia and leukopenia

DRUG INTERACTIONS

Cytochrome P450 Summary

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see **Boxed Warning, Contraindications**].

An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

Cyclosporine A

The concomitant administration of bosentan and cyclosporine A is contraindicated [see **Contraindications**].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Co-administration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A substrate) by approximately 50%.

Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered [see **Contraindications**].

Co-administration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

In vitro data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A and CYP2C9. Ritonavir inhibits OATP and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on OATP.

In normal volunteers, co-administration of Tracleer 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone. Therefore, adjust the dose of Tracleer when initiating lopinavir/ritonavir [see **Dosage and Administration**].

Co-administration of Tracleer 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

Simvastatin and Other Statins

Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that are significantly metabolized by CYP3A, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A-metabolized statins should have cholesterol levels monitored after Tracleer is initiated to see whether the statin dose needs adjustment.

Rifampin

Co-administration of bosentan and rifampin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose (likely due to inhibition of OATP by rifampin), but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure liver function weekly for the first 4 weeks before reverting to normal monitoring.

Tacrolimus

Co-administration of tacrolimus and bosentan has not been studied in humans. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together.

Ketoconazole

Co-administration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold in normal volunteers. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered.

Warfarin

Co-administration of bosentan 500 mg twice daily for 6 days in normal volunteers, decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients.

Digoxin, Nimodipine, and Losartan

Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

Sildenafil

In normal volunteers, co-administration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. The changes in plasma concentrations were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost

In a small, randomized, double-blind, placebo-controlled study, 34 patients treated with bosentan 125 mg twice daily for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X: Teratogenic Effects [see Contraindications]

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Females of childbearing potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

Drug interaction studies show that Tracleer reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients using Tracleer and should not be used as a patient's only contraceptive method [see **Drug Interactions**]. Females of childbearing potential using Tracleer must use two reliable forms of contraception unless she has a tubal sterilization or has a Copper T 380A IUD or LNg 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/ m^2 basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m^2 basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs [see **Nonclinical Toxicology**].

Nursing mothers

It is not known whether Tracleer is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration, Warnings and Precautions**].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Patients with Low Body Weight [See Dosage and Administration].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m^2 basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m^2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

Important Information

- Monthly monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

- Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

- Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

Manufactured for: Actelion Pharmaceuticals US, Inc. South San Francisco, CA 94080, USA
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References for previous pages: 1. Data on file, Actelion Pharmaceuticals.

ACTELION

First Factor Xa Inhibitor Approved for DVT Prevention

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

With the recent approval of rivaroxaban for an orthopedic indication, there are now two new oral anticoagulants available in the United States, after a more-than-half-century lapse since warfarin was approved.

The Food and Drug Administration approved rivaroxaban (a factor Xa inhibitor that is taken orally) for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery. The recommended dosage is 10 mg orally, once daily, for 35 days in patients undergoing hip surgery and for 12 days for those undergoing knee surgery. The initial dose should be taken at least 6-10 hours after surgery, "once hemostasis has been established," according to the prescribing information.

Rivaroxaban is the first drug in this class to be approved. Dabigatran, an orally administered direct thrombin inhibitor marketed as Pradaxa by Boehringer Ingelheim Pharmaceuticals, was approved for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in 2010 – the first oral anticoagulant approved since warfarin was approved in 1954. Neither requires international normalized ratio monitoring.

Rivaroxaban is a small-molecular-weight drug that works by inhibiting direct factor Xa, which lowers thrombin production and prolongs prothrombin time. At a meeting in 2009, the FDA's Cardiovascular and Renal Drugs Advisory Committee voted 15-2 that the data from clinical trials demonstrated that the drug had a favorable risk-benefit profile for this indication. At the meeting, panelists were concerned that the drug might be used off label, and stressed that clinicians should avoid prescribing the drug for longer periods and for unapproved indications.

The drug is also being studied in patients with acute coronary syndrome. The manufacturer, Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson, is marketing the drug as Xarelto.

More than 6,000 patients undergoing hip or knee replacement surgery have been treated with rivaroxaban in clinical trials, according to the FDA statement announcing the approval.

Among patients undergoing knee replacement surgery, almost 10% of those who were treated with rivaroxaban had a venous thromboembolic event (VTE), compared with 18.8% of those who were treated with enoxaparin (Lovenox), according to the statement. In two studies of patients undergoing a hip replacement, 1.1% and 2% of patients who received rivaroxaban developed a VTE, compared with 3.9% and 8.4% of those who received enoxaparin, respectively.

Bleeding was the most common adverse event associated with rivaroxaban. The label includes warnings about the increased risk of bleeding that can be serious and fatal, as well as a boxed warning about the risk of a spinal or epidural hematoma in surgical settings in patients who are anticoagulated and are receiving neuraxial anesthesia or undergoing a spinal puncture. The manufacturer has been asked to conduct a postmarketing study on the risk factors, clinical management, and outcome of major bleeding cases associated with rivaroxaban use, according to the FDA's approval letter.

Rivaroxaban "doesn't appear to have a great liability in patients with organ impairment, so it can be used in patients with mild or moderate renal or hepatic dysfunction," Dr. Peter Kowey said in an interview. There is a large amount of information available on rivaroxaban for various indications, "and like dabigatran, the once-a-day dosing will have an impact on compliance," he added. The two drugs, however, cannot be directly compared because there are no head-to-head studies of the two drugs, and cross-study comparisons are treacherous, noted Dr. Kowey, a cardiologist and professor of medicine and clinical pharmacology at Jefferson Medical College, Philadelphia.

With the possible approval of other novel anticoagulants over the next 1-2 years, the choice of which one to prescribe may prove to be a challenge for clinicians. The potential for additional new anticoagulants on the market "will create a tremendous burden" to provide the education, information, and other resources that physicians will need "in order to make an intelligent decision about choice of therapy," he said. These drugs have different mechanisms of action, pharmacologies, drug interactions, and dosing schemes – and dosing of the same drug differs by indication, "so there's a lot to learn and a lot to digest when choosing one of these new drugs for an individual patient," he said.

The availability of these newer agents will result in a lot more patients being anticoagulated, "some appropriately," Dr. Kowey said. However, there is concern that because of the excitement over these new anticoagulants, some low-risk patients who probably should not receive anticoagulants will end up on treatment.

Although he expects that the use of warfarin will "diminish dramatically" with the availability of these new anticoagulants, warfarin will continue to be used to treat certain patients, such as those in whom it is important to know their precise level of anticoagulation for various reasons (such as a history of bleeding), and for indications for which the new anticoagulants have not yet been proved to be safe and effective (such as mechanical heart valve prophylaxis or treatment of pulmonary embolism). And there are those clinicians – and patients – who prefer to wait until the newer drugs have been available for awhile before they switch, he said.

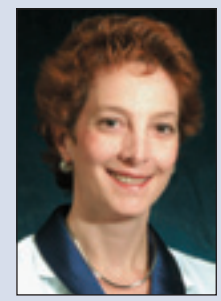
Dr. Kowey said that another possible benefit of having several agents on the market is that competition will reduce their costs.

A Johnson & Johnson spokesperson said that the cost of rivaroxaban is $6.75 a day, the same as dabigatran in November 2010.

Dr. Kowey consults for every company that is developing a new anticoagulant: J&J, Merck, Portola, BMS, Daiichi-Sankyo, Boehringer Engelheim, Sanofi, and AstraZeneca. He is not an investigator for any and he does not own stock – all fee for service consultation. ■

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: This article brings information regarding the approval of another new oral anticoagulant. Rivaroxaban, a direct inhibitor of factor Xa, has been approved for DVT prophylaxis in orthopedic patients with expectations for additional indications in the near future. This drug joins dabigatran, another oral anticoagulant approved last year for prevention of ischemic stroke.



Neither of these drugs require INR monitoring; however, they cost much more than warfarin. There are no comparative studies available at present between these drugs, or between the newer agents and warfarin in terms of safety and efficacy. The addition of newer agents to the market is always exciting. Their niche will need to be determined, and their use should be informed and carefully considered.

After Heart Transplantation: Live High, Live Longer

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS – Heart transplant recipients living at altitude have better survival, compared with those residing closer to sea level, according to a large observational study.

This retrospective analysis of the UNOS (United Network of Organ Sharing) database included 36,529 adults who received a heart transplant during 1990-2008. Investigators assigned each patient a residential altitude based on home zip code.

A survival advantage became apparent at an altitude of 2,000 feet above sea level, and was even more pronounced for the 1,029 patients who lived at an elevation higher than 4,000 feet, Dr. Curtis J. Wozniak reported at the annual meeting of the Western Thoracic Surgical Association.

After controlling for diabetes, tobacco use, transplant urgency status, age, peak oxygen intake, and other potential confounders in a multivariate regression analysis, the researchers found that patients who lived at an elevation above 4,000 ft were 22% less likely to die during their first year post transplant than were the 34,221 living below 2,000 feet. They were 15% less likely to have died within 5 years and 16% less likely to be dead at 10 years.

Patients living at 2,000 feet or above were 18% less likely to die within 1 year and 7% less likely to die within 5 and 10 years than were those at lower altitudes, added Dr. Wozniak of the University of Utah, Salt Lake City.

Their findings were unexpected. In fact, the study hypothesis was that heart transplant recipients living at altitude would have reduced survival. The investigators' reasoning was that even at moderate altitudes, altitude-induced hypoxia would result in pulmonary vasoconstriction and right ventricular hypertrophy.

The mechanism for the unexpected survival benefit is unclear. Pulmonary artery pressures were actually lower on average in patients living at altitude, but the logistic regression analysis suggested that pulmonary hypertension cannot explain all of the observed survival difference between the two groups of patients, Dr. Wozniak said.

He noted that his results are consistent with those of a recent analysis by British investigators, who found that ischemic heart disease mortality among Americans living at an altitude above 1,000 m was 4-14 fewer per 10,000 people than for those living within 100 m of sea level (J. Epidemiol. Community Health 2011 March 15 [doi: 10.1136/jech.2010.112938].

Dr. Wozniak declared having no financial conflicts. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: It would be helpful to see changes in mortality in quintiles instead of above or below 4,000 feet, as we also know that the University of Colorado and the University of Utah are excellent transplant centers. It is also important to determine patients' compliance with follow-up visits and medical treatment.

Pages 20a—20b

Beware Cardiac Arrest After Pneumonia Admission

BY NASEEM S. MILLER
Elsevier Global Medical News

DENVER – Patients with pneumonia may be at risk of sudden cardiovascular collapse within the first 72 hours after admission to the hospital, according to the preliminary findings of a large retrospective analysis.

In addition, almost one in five of those in-hospital cardiac arrests (IHCA) occurred outside of the ICU, and many of the patients were not receiving critical care interventions prior to the cardiac arrest, the study investigators found.

The findings "may indicate that current triage practices or other processes of care are inadequate," they said (Am. J. Respir. Crit. Care Med. 2011;183:A6339).

The study is the first of its kind to analyze the characteristics of in-hospital cardiac arrest among pneumonia patients, lead author Dr. Gordon E. Carr said at a briefing at an international conference of the American Thoracic Society.

Patients with pneumonia are at risk of following a progressive pathway of severe sepsis, septic shock, and multiple organ failure before having a cardiac arrest, Dr. Carr noted. However, some patients go from developing severe infection straight to cardiopulmonary collapse. Several clinical and epidemiologic studies have shown that not all patients with sepsis go down the typical pathway (Curr. Opin. Anaesthesiol. 2008;21:128-40).

Dr. Carr and his colleagues at the University of Chicago Medical Center conducted the retrospective analysis using the American Heart Association's Get With The Guidelines–Resuscitation database. The data covered 9 years and included about 500 North American hospitals.

The team analyzed 166,919 cardiopulmonary arrest events, 44,416 of which occurred within 72 hours after admission. They focused on 5,367 events in which patients had pneumonia as a preexisting condition prior to having their first pulseless event after hospital admission.

The median time from admission to IHCA was 20.7 hours. Only 14.7% of patients with pneumonia and IHCA survived to discharge. Also, 19.3% of the IHCA events occurred in a general inpatient area, while 77.2% occurred in an intensive care or step-down unit.

The analysis showed that arrhythmia was the most common cause of IHCA (65%) among that group of patients, followed by respiratory insufficiency (53.9%), and hypotension/hypoperfusion (49.8%).

Most of the rhythms were not "shockable," said Dr. Carr, including pulseless electrical activity (45.2%), asystole (38.4%), and tachycardia (16.4%).

The study's limitations included its use of a large database, and "any huge set of data is going to have the inherent problem in terms of bias," Dr. Carr said. Also, the researchers couldn't adjust for the severity of pneumonia and had no information on the processes of care.

The take-away message for physicians is "to be alert to the possibility of abrupt collapse in pneumonia patients," and monitor those patients with comorbidities carefully, Dr. Carr cautioned.

Dr. Carr had no disclosures. ■

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: It is a very interesting observation that many patients admitted for pneumonia developed cardiac arrest within 72 hours of their hospitalization and had significant mortality (85% of the patients). However, it is unclear if these events occur because seriously ill patients are not identified at the time of admission according to current severity illness scores and are therefore inappropriately admitted to non–intensive care units. Another possibility is that some patients may have worsened during their initial hospitalization and this worsening is not detected until the complications occur. Further research is needed to address the impact of cardiovascular events in patients with pneumonia.

SSRIs Can Affect Fetal Pulmonary Development

BY SUSAN LONDON
Elsevier Global Medical News

VANCOUVER, B.C. – The impact of selective serotonin reuptake inhibitors on fetal pulmonary vascular physiology may boil down to genetics, study results suggest.

In a study of 55 pregnant women who were near term, a variety of right pulmonary artery measures (such as flow and impedance) did not differ significantly between fetuses of women who had been taking SSRIs since conception and those of women who had not. There was also no measurable effect of acute exposure to SSRIs.

However, within the SSRI-exposed group only, fetal right pulmonary artery flow was about 40% higher for infants who experienced respiratory distress in the neonatal period than for their counterparts who did not.

"So there is something different about this particular group in terms of the fact that they developed respiratory distress," said lead investigator Dr. Kenneth Lim. "Maybe they respond to the SSRIs differently; maybe there is a genetic polymorphism that makes them more susceptible."

This difference can be tapped to elucidate the effects of in utero exposure, he added. "Maybe we need to look at that a little bit more closely in the next phase of our studies, to try to determine whether there is something going on in the pulmonary system of these babies."

Previous studies have determined that maternal use of this class of drugs has a variety of deleterious effects on the infant, including low birth weight, prematurity, and a type of withdrawal syndrome characterized by irritability.

"But interestingly, there is also a link with respiratory distress, which tends to be more like a TTN [transient tachypnea of the newborn]–type respiratory distress, and also, there have been case reports of primary pulmonary hypertension," according to Dr. Lim of the University of British Columbia in Vancouver.

The pathogenesis of these pulmonary abnormalities is unclear. "We do know that serotonin itself is a very powerful vasoconstrictor, but it has differential effects in different tissues," Dr. Lim explained at the annual meeting of the Society of Obstetricians and Gynaecologists of Canada.

Preclinically, serotonin impairs lung fluid resorption, suggesting that SSRI-exposed infants may be unable to reabsorb lung fluid after birth; one SSRI has been found to increase arterial smooth muscle cell proliferation.

Pregnant women were eligible for the study if their fetus did not have any anomalies, if they were not taking any drugs other than SSRIs, and if they did not have any serious medical conditions. The nonexposed control group consisted of healthy women who had not taken SSRIs during pregnancy. The exposed group consisted of women with a mood disorder who had been taking SSRIs since the time of conception.

At a gestational age of about 36 weeks, the women underwent a morning ultrasound to assess fetal pulmonary vasculature. Those taking an SSRI then took their medication for the day. In the afternoon, all women had a second ultrasound.

This approach allowed assessment of the effects of both chronic SSRI exposure (by comparing exposed and nonexposed groups) and acute SSRI exposure (by comparing morning and afternoon measurements), Dr. Lim explained.

Results were based on 23 women taking SSRIs (predominantly fluoxetine) and 32 control women. They were 33 years old, on average.

At delivery, the gestational age was significantly younger in the SSRI-exposed group (39.0 vs. 40.0 weeks). Additionally, the SSRI-exposed infants had a smaller head circumference (34.1 vs. 35.0 cm) and poorer Apgar scores at 1 minute (7.5 vs. 8.4). Infants in the SSRI-exposed group also were more likely to have respiratory distress (30% vs. 3%) and jitteriness (39% vs. 3%).

When it came to fetal right pulmonary artery parameters, there were no significant differences between SSRI-exposed and SSRI-nonexposed groups, or between morning and afternoon within the exposed group, in terms of pulsatility index, resistance index, peak systolic velocity, diameter, area, and flow.

However, within the SSRI-exposed group, fetal right pulmonary artery flow was higher for infants who experienced respiratory distress in the neonatal period than for those who did not, with a value of approximately 280 mL/min vs. 175 mL/min ($P = .03$).

Dr. Lim had no disclosures. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Maternal use of SSRIs during pregnancy may be a factor in the development of transient tachypnea of the newborn and possibly affect pulmonary vascular blood flow. Pediatric pulmonologists should think about investigating this history in a newborn with respiratory problems.

IGRAs Are TB Test Alternative After Age 5 Years

BY BRUCE JANCIN
Elsevier Global Medical News

VAIL, COLO. – Interferon-gamma release assays offer significant advantages over conventional tuberculin skin testing under certain circumstances, but not in children younger than 5 years old.

The IFN-gamma release assays (IGRAs) have not been well studied in children younger than age 5 years, but the available data suggest that the test results are less reliable in this age group. Given the high rate of progression from latent to active disease as well as the high rates of severe disease in this younger population, the Centers for Disease Control and Prevention recommends using the tuberculin skin test (TST) for these young children, Dr. Donna Curtis said at a conference on pediatric infectious diseases sponsored by Children's Hospital Colorado.

Beyond age 5 years, however, the sensitivity and specificity of IGRAs and the TST are similar, and the tests can be used interchangeably, added Dr. Curtis of the University of Colorado at Denver.

IGRAs are blood tests that measure IFN-gamma production by WBCs in response to stimulation by TB antigens. The two Food and Drug Administration–approved IGRAs on the market are Cellistis's QuantiFERON–TB Gold In-Tube test and Oxford Immunotec's T-SPOT.TB test. The test results are reported from the laboratory as positive, negative, or indeterminate.

Among the IGRAs' advantages are that only a single patient visit is required and results are available 24 hours after laboratory processing. Also, there are no false-positives due to previous BCG (bacille Calmette-Guérin) vaccination, a big problem with TSTs in foreign-born patients. And unlike the TST, there is no boosting phenomenon with repeated IGRA tests.

On the other hand, an IGRA requires fresh blood and plenty of it – four tubes' worth – and it must be transported promptly to the laboratory for processing. The cost, albeit variable, is often more than that of a TST.

An IGRA is clearly the preferred test in patients older than age 5 years who have received a BCG vaccine, and in those with a reduced likelihood of returning for a second visit to have their TST read.

The CDC recommends both the IGRA and TST in patients whose first test is negative but who have a high risk of infection or progression to active disease.

Dr. Curtis noted that a recent Croatian study involving 142 BCG-vaccinated children younger than age 5 with a known TB exposure – all of whom had both a TST and IGRA – found a high rate of discordant results. The investigators concluded that both tests should routinely be used in this age group, and that a child should be considered infected if either or both results are positive (Pediatr. Infect. Dis. J. 2011 May 12 [doi: 10.1097/INF.0b013e318220c52a]).

However, Dr. John W. Ogle said that the dual-test strategy for younger children is fraught with problems.

"There are no normative data for IGRAs in kids under age 5 years. The IGRAs are standardized on adult patients. The amount of interferon that you make in response to an antigen is age dependent; kids less than age 5 make much less compared to adults. So if you do an IGRA in a young kid, you're much more likely to have a false-negative result," explained Dr. Ogle, professor and vice chair of pediatrics at the University of Colorado at Denver and director of pediatric services at Denver Health Medical Center.

A year ago, the CDC issued updated guidelines for the use of IGRAs (MMWR 2010;59[RR-5]:1-25).

Dr. Curtis reported having no relevant financial conflicts. ■

Coinfection With RV Ups Risk

RSV • *from page 1*

which some researchers contend is of use. Moreover, the findings suggest that hospitals consider adding RV to respiratory viral panels, he said.

The 16-center study enrolled consecutive children between November and March during 2007-2010. Of the 2,207 children enrolled, 83% were located on the ward while 17% were admitted to the intensive care unit. Of those 377, 42% were intubated or given continuous positive airway pressure. Overall mean length of stay was 2 days. The patients had a median age of 4 months; 59% were male, 61% were white, 24% black, and 15% other races. A third (36%) were of Hispanic ethnicity.

The three most common viral etiologies identified by polymerase chain reaction were RSV-A (43%), RSV-B (30%), and RV (26%). Adenovirus, human metapneumovirus, and the coronaviruses were all 7%-8%, and only 6% of the children had no virus detected. (These figures add up to more than 100 because of a 30% rate of coinfections.) The low-frequency infections did not affect results, so subsequent analysis focused on RSV (subtypes A and B) and RV, Dr. Mansbach said.

Of the 940 children in whom RSV-A was identified, it was the only virus in 66%, while one or more additional viruses were identified in the other 34%. Similarly, 68% of the 664 RSV-B infected patients had only one virus identified, while 32% were coinfected.

Rhinovirus was somewhat different, however, in that just 30% of 564 had only that and 70% had coinfections.

For children with both RSV-A and RSV-B, the likelihood of having a length of stay of 3 or more days did not differ between those who had the single virus infection and those who were coinfected (48% vs. 49%, respectively, for RSV-A, and 47% and 54% for RSV-B). There was a significant difference with rhinovirus, however, with 28% of those with the single infection and 46% with coinfections hospitalized 3 or more days.

After adjustment for age, gender, race, eczema history, intubation history, apnea, retractions, oxygen saturation, oral intake, comorbid medical condition, and site, rhinovirus alone was associated with a lower chance of being hospitalized 3 or more days compared with RSV-A or RSV-B alone (odds ratio 0.4), while RSV-RV coinfections were associated with a significantly greater chance of being hospitalized for that duration compared with RSV-A or RSV-B alone (OR 1.3).

Clustering by site did not affect the results, and in a preliminary analysis, controlling for acute severity as defined by ICU, CPAP, or intubation also did not materially change the results, Dr. Mansbach said.

This study was conducted as part of the Multicenter Airway Research Collaboration, a program of the Emergency Medicine Network. Pediatric Research in Inpatient Settings sites collaborated with EMNet, Dr. Mansbach said. He reported having no relevant financial disclosures. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Dr. Gern in Wisconsin and Dr. Sly in Australia have shown rhinovirus (RV) present in PCR analyses of children's nasopharyngeal secretions during acute asthma exacerbations. Some have debated if this association is causative or coincidental, the result of a subclinical viral infection, on par with bacterial colonization. The present study suggests that RV, in coinfection with respiratory syncytial virus (RSV), causes a more prolonged illness than RSV infection alone. Furthermore, RV was present alone only 30% of the time, when isolated in a child under age 2 hospitalized with bronchiolitis, with coinfections being the more common presentation. It seems we are still only beginning to understand the role of RV in respiratory illnesses.

PRESIDENT'S REPORT
The Year in Review

"If life were measured by accomplishments, most of us would die in infancy." – A. P. Gouthey
("By these standards, the ACCP is already a venerable elder." – D. D. Gutterman)

In my final message as President, it is appropriate to reflect on the many accomplishments at the ACCP over the past year. Although our progress has been highly integrated to achieve the updated Board-approved *ACCP Strategic Plan 2011-2012,* in the interest of readability, I will highlight, *in no particular order,* discrete milestones achieved by ACCP members and staff that serve as a foundation for initiatives planned for 2012 and beyond.

BY DR. DAVID D. GUTTERMAN, FCCP

1. The Reality of Simulation. The ACCP is at the forefront of chest medicine education with simulation as a signature product. Sessions offered at CHEST are always popular, but even sessions at the Northbrook headquarters have been fully subscribed with members clamoring for more. To this end, we are in the process of:

▶ Increasing our capacity to conduct simulation by expansion of our physical facility;

▶ Exploring new opportunities in chest medicine where simulation training is needed; and

▶ Growing the cadre of faculty who are experienced at delivering quality simulation training, through our "train-the-trainer" program.

2. Leadership Continuity. The four Presidents (4P) concept has matured during the past year and is emerging as an effective way to govern the ACCP. Each week, all four members of the presidential lineage, along with our CEO, strategize, discuss, and plan current activities and address issues/concerns by conference call. This provides an important breadth of input and serves to keep everyone informed and in agreement with planned approaches to mission-critical issues. Some weeks, we invite other members of leadership to join the calls and, quarterly, we include Past Presidents on the call. The Past Presidents have been an extremely helpful source of collective historical wisdom that has been influential in guiding major new initiatives and providing direction for complex decisions.

3. CHEST Foundation OneBreath™ Campaign. The widely anticipated OneBreath Campaign was launched this year, replete with an exciting new Web site and multiple opportunities for social networking in support of chest medicine. This campaign will move into full swing during the next year but The Foundation staff and trustees are to be commended on an exciting, timely, and highly successful debut.

4. International Development. Our international efforts have been streamlined and strategically focused over the past 2 years on China, Middle East, South America, and India. As a result, many new opportunities have emerged.

▶ This year at CHEST, global day will begin with a lecture by Dr. Chen Wang, President of the Chinese Respiratory Society. Dr. Chunxue Bai, ACCP Regent for China and President of the Shanghai Respiratory Society, will co-chair the session. China has had the fastest growing increase in ACCP membership and attendance at CHEST of any country.

▶ In the Middle East, we have held two highly successful meetings jointly with the Gulf Thoracic Society. This year, we will continue that collaboration but have also initiated a program with the International Medical Center in Jeddah, Saudi Arabia, for a separate educational conference. We are pursuing a long-term partnership for subsequent years.

▶ We are also excited about a first-time ever Israel Respiratory Society-ACCP joint conference to be held in Tel Aviv in March 2012, with an opportunity for subsequent programs.

▶ Some of our greatest successes have been in India, where we are in the process of concluding long-term contracts to provide a variety of educational curricula for Indian respirologists.

5. Organizational Structure. Several major changes to the structure of the ACCP have been implemented this year. The driving force was the need to better align the College's infrastructure with our new strategic plan and to provide a means for involving more members and supporting integration, collaboration, and harmonization throughout our organizational structure. To this end, we have:

▶ Approved a new ACCP strategic plan and revised the ACCP bylaws.

▶ Revitalized the Council of Governors and provided clarity with regard to expectations and goals.

▶ Completed the work of the Presidential Task Force on Diversity and Disparities. This task force, led by Dr. Marilyn Foreman, FCCP, and Dr. Sola Olopade, FCCP, created a comprehensive, forward-thinking proposal to enhance the ACCP by making diversity and inclusiveness a central component of all College activities and to put the ACCP at the forefront in this area. As a result of their work, the Board approved: a new standing committee, the Committee on Diversity, to implement the recommendations of the Presidential Task Force; a change in the ACCP vision statement to reflect this new approach.

▶ Implemented the SWAT (strategic work action team) to assess, consult, and advise the Board of Regents regarding requests from other societies. The SWAT broadly represents all aspects of the College, and its involvement ensures that all major questions get addressed by those with the proper expertise.

▶ Established the Chest Medicine Affairs (CMA) committee. This committee will manage advocacy initiatives, including regulatory and legislative issues. Members will also plan strategic advocacy sessions for the ACCP. The committee membership is composed primarily of Governors and includes representation of each of the 10 regions throughout the United States as designated by the Centers for Medicare & Medicaid Services.

▶ Reorganization of the NetWorks. Changes in NetWork structure are under consideration after excellent feedback from the Council of NetWorks and Board of Regents this summer. Plans are to roll out new approaches for linking members with content expertise in a way that provides greater opportunities for individual members, better integrates the NetWork system into other facets of College activity (Governors, CHEST meeting, advocacy, etc), and provides greater value to our members.

6. Communication. The majority of challenges I have encountered as President involved failed or insufficient communication. It is best to communicate frequently, effectively, and proactively. Realizing that no single form of communication is used by all individuals, we are in the process of developing new communication tools to allow greater input and engagement by members. Although many of the needed advances await a new electronic association management system (AMS), we have moved forward on two initiatives already:

▶ Establishing a Presidents' blog. This is a means for allowing input from members on a variety of complex issues or to provide informational content.

▶ Weekly ACCP newsletter updates *(ACCP NewsBrief)*. This e-mail highlights key activities and news from the ACCP and elsewhere in chest medicine. Members can opt out if they prefer.

7. COPD Alliance. The ACCP was instrumental in organizing a novel nationwide educational and informational curriculum devoted to increasing awareness about COPD. This is a joint effort among health-care societies, industry, primary care practitioners, and communities to improve the quality and consistency of care for patients with COPD. This multimillion dollar initiative has been launched, and results will be forthcoming.

Consistent with my theme of integration, harmonization, and collaboration, no one person can take credit for our successes (although the President is a highly visible and frequently attractive target for criticisms regarding our failures). It is the combined effort of an outstanding ACCP staff, superb and dedicated colleagues within the Presidential lineage and the Board of Regents, and the breadth of other extraordinarily effective ACCP leaders serving on committees, task forces, and councils who have been responsible for those achievements mentioned above. I am humbled to have served as President of the ACCP during the past year. This has been the most rewarding professional experience of my life! Even as it comes to an end, I grow even more excited about our future with Dr. Suhail Raoof, followed by Dr. Darcy Marciniuk at the helm. ■

Join the Ambassadors Group Today!

Composed of ACCP members, their spouses, and friends, The CHEST Foundation's Ambassadors Group is actively recruiting members. Ambassadors Group members support the mission of The CHEST Foundation – to provide resources to advance the prevention and treatment of diseases of the chest – in a variety of ways, including:

▶ Educating elementary school students about the importance of lung health and dangers of tobacco use.

▶ Creation of a lending library, which offers educational materials to enhance The CHEST Foundation's Lung Lessons℠ program.

▶ Raising funds by selling "Love Your Lungs®" wristbands, note card sets using past poster contest winners designs displaying the theme "Love Your Lungs," and tote bags.

▶ Donating funds to support the annual Ambassadors Group Humanitarian Award.

▶ Social activities for ACCP spouses and/or guests at the annual CHEST meeting.

THE CHEST FOUNDATION® AMBASSADORS GROUP

Individuals can join this active group in one of three membership categories: $50 for US and Canadian adults, $35 for international adults, $10 for high-school and college youth.

Join the Ambassadors Group today at www.onebreath.org/page.

Volunteering. Educating. Networking. ■

E ʻai ka-kou! Bon Appétit, Hawaiian Style

With CHEST 2011 only a month away, you may be starting to wonder, "Where's a good place to eat in Hawaii?" It's always nice to know where you can get a great meal.

To help you know just where to go, your ACCP colleagues who live in Hawaii have shared some of their favorite places for a meal, quick bite, and cup of kona.

Favorite Restaurants

Asian Fusion

▶ 3660 On the Rise
3660 Waialae Ave,
Honolulu
(808) 737-1177
3660.com

▶ Alan Wong's
1857 S. King Street,
Honolulu
(808) 945-6573
alanwongs.com

▶ Chef Mavro
1969 South King Street,
Honolulu
(808) 944-4714
chefmavro.com

▶ Morimoto Waikiki
1775 Ala Moana Blvd,
Honolulu
(808) 943-5900
morimotowaikiki.com

▶ Nobu Waikiki
2233 Helumoa Road,
Honolulu
(808) 237-6999
noburestaurants.com

▶ Roy's—Hawaii Kai (original)
6600 Kalanianaole Highway, Honolulu
(808) 396-7697
roysrestaurant.com

▶ Roy's—Waikiki Beach (close to convention center)
226 Lewers Street,
Honolulu
(808) 923-7697
roysrestaurant.com

Sushi

▶ Gazen Izakaya
2840 Kapiolani Blvd,
Honolulu
(808) 737-0230

▶ Miyabi Sushi
808 Kapahulu Ave,
Honolulu
(808) 737-2828
miyabi-hawaii.com

▶ Sushi Izakaya Gaku
1329 S King St, Honolulu
(808) 589-1329

CHEST 2011

October 22 - 26
Honolulu, Hawaii

Chinese

▶ P.F. Chang's
1288 Ala Moana Blvd,
Honolulu
(808) 596-4710
pfchangshawaii.com

Italian

▶ Taormina
227 Lewers Street,
Honolulu
(808) 926-5050
taorminarestaurant.com

Hawaiian, American

▶ Duke's Restaurant & Barefoot Bar
2335 Kalakaua Ave,
Honolulu
(808) 922-2268
dukeswaikiki.com

Favorite Place for a Quick Bite

▶ Fat Boys Kailua
301A Hahani Street,
Kailua
(808) 263-2697

▶ Fat Boys Waipio
94-1221 Ka Uka Boulevard,
Waipahu
(808) 680-7520

▶ Goma Tei Ramen
Ala Moana Center
1450 Ala Moana Blvd,
Honolulu
(808) 947-9188

▶ Kaka'ako Kitchen
Ward Centers
1044 Auahi Street,
Honolulu
(808) 596-7488

▶ Makai Market Food Court
Ala Moana Center
1450 Ala Moana Blvd,
Honolulu

▶ Side Street Inn on Da Strip
614 Kapahulu Ave,
Honolulu
(808) 739-3939

▶ SushiSan
1409 Kapiolani Blvd,
Honolulu
(808) 944-0670

▶ Zippy's Ala Moana
1450 Ala Moana Blvd,
Honolulu
(808) 973-0870
multiple other locations

Not So Quick, But Nice Lunch

▶ Mariposa Restaurant (at Neiman Marcus)
Ala Moana Center
1450 Ala Moana Blvd,
Honolulu
(808) 951-3420

Favorite Place for Kona (Coffee)

▶ Alan Wong's Restaurant

▶ Aloha Tower Market Place

▶ Coffee Bean and Tea Leaf

▶ Coffee Gallery, Hale'iwa

▶ Starbucks

CHEST 2011 is next month, October 22-26 in Honolulu, Hawaii. After October 3, registration will be available online only or on-site (beginning October 21). Learn more about CHEST 2011 at www.accpmeeting.org.

Mahalo to the ACCP members who shared their favorite places. ■

Product of the Month

ACCP Board Review e-Book Collection

From the ACCP Board Review 2009 courses come these interactive online resources, the latest tool in the ACCP's comprehensive study program. Every topic is covered in a concise, easy-to-use format with many enhanced review options.

▶ Navigate valuable board review content easily, with a user-friendly, interactive online format.

▶ Find topics of interest fast, with advanced keyword search capabilities, integrated with other ACCP online publications, including *CHEST*.

▶ Obtain referenced articles quickly, with fully linked-out annotated bibliographies.

Use as self-study resources to prepare for the critical care medicine, pulmonary medicine, and sleep medicine sub-specialty board examinations.

See the details www.chestpubs.org/. ■

Attend the OneBreath™ Luau

Sunday, October 23
6:00 PM – 9:00 PM
Hilton Hawaiian Village Lagoon Green

Hau oli ka mana o i ka ho okipa ana mai ia oe i ane i
Translation: We are pleased to welcome you!

Join your colleagues and friends on a journey through the islands of Polynesia for The CHEST Foundation's OneBreath Luau. The sound of the conch, the beat of the drums, and the echoes of the Hawaiian chant will signal the start of the luau, complete with traditional entertainment and food.

This festive evening will include a very special lei greeting, the exotic and delicious flavors of authentic Hawaiian cuisine served family style, and an exciting performance by Hawaiian entertainers. Stroll among Hawaiian artisans as they demonstrate their crafts, including a lei maker, lauhaula weaver, coconut weaver, poi pounder, tapa cloth maker, and wood-carver.

The OneBreath Luau promises to be an exciting and enchanting evening, while raising funds to support the OneBreath campaign and OneBreath.org, which features nine prevention areas and the *OneBreath™ Family Activities Toolkit*. Learn More at OneBreath.org.

Donors to the OneBreath campaign will be eligible for complimentary tickets. Donate $500 to be eligible for one luau ticket, and donate $1,000 or more to be eligible for two tickets.

Registration Now Open
Adults (12 and older) $150
Children (aged 3-11) $75
Register at: http://2011.accpmeeting.org/program/onebreath-luau or contact Lee Ann Fulton @ lfulton@chestnet.org, or (847) 498-8332 for more information. ■

The CHEST Foundation encourages you to join its OneBreath™ campaign during CHEST 2011 at OneBreath.org. Anyone becoming a member during CHEST 2011 will be entered into a raffle to win an Apple iPad® 2 with Wi-Fi.

NETWORKS

COIs, Airway Resistance, Bioengineered Lungs

Members in Industry

Consciousness of "Other" Financial Conflicts of Interest

Over the past 2 decades, conflicts of interest in health care (COI-H) have drawn increasing scrutiny. The primary COI-H discussed has been between physicians and commercial interests, such as pharmaceutical or device industries. Attention has focused on the potential for gifts and additional income to cause the interests of physicians to diverge from those of their patients. This concern has led to many journal articles, an Institute of Medicine white paper, state laws, and a range of institutional and journal policies forbidding certain activities and/or mandating disclosure.

Other activities with the potential for COI-H warrant attention, such as the following:

- Influence of practice setting (eg, multispecialty, hospital owned) on referral patterns, formulary committee decisions, etc
- Responsibilities of authors to disclose personal and institutionally owned intellectual property
- Pressure for academics to "publish or perish," and at what expense

These issues are impossible to fully address in this brief discussion but warrant our attention in daily practice and medical leadership activities. Disclosure of relevant information should be standard, and we should be vigilant in reminding one another and ourselves about the risk of misaligned goals.

Where possible, representatives of the patient community should participate in policy generation and execution. COI-H are unavoidable, yet manageable, with conscious, continuous, and conscientious effort.

Dr. Mark Forshag, FCCP
NetWork Ex Officio

Practice Operations

CHEST 2011: Top Picks in Practice Management

Feeling overwhelmed and unprepared to navigate the rapidly changing landscape in health care? If you answered "yes," you are similar to most members and not alone in your quest for the knowledge and skills to formulate strategies for the future. CHEST 2011 offers ample opportunities for participants to educate themselves on practice management topics. Session attendees will have the further benefit of networking with leading experts in physician management, physician-hospital alignment, electronic health records implementation, reimbursement, Physician Quality Reporting System, meaningful use, coding, and practice operations. It is by far the best annual opportunity for chest physicians and administrative staff to get ahead of the power curve.

To learn more…

Oct 22, 7:30 AM – 4:30 PM: Postgraduate Multipass Course: Navigating Health-care Reform: A Practical Guide to Business Tools and Quality Improvement
Oct 23, 3:00 PM – 4:15 PM: Members in Industry NetWork Open Meeting: Profit as a Driver of Innovation in the Pharmaceutical Industry: Friend or Foe?
Oct 24, 7:15 AM – 8:45 AM: Practice Operations NetWork Open Meeting: Medicare's Perspective: Compliance Tips, CMS Initiatives, and Fair Reimbursement in the Affordable Care Act Era – with guest Dr. Arthur Lurvey
Oct 24, 11:00 AM – 12:30 PM: Choosing (or Changing) Your Career Path: Honest Sales Pitches for Private Practice, Research, Industry, and More
Oct 24, 11:00 AM – 12:30 PM: How to Run a Sleep Center in 2011
Oct 24, 1:30 PM – 2:45 PM: How to Run a Sleep Center: Accreditation Issues
Oct 24-25, 2:30 PM – 1:30 PM: Roundtables in the Clinical Resource Center: Coding and Reimbursement, EHR, ACOs, Using NPPSs in Your Practice, General Practice Management/Business of Medicine
Oct 24-26, By appointment: One-on-One Consultations with Diane Krier-Morrow in the Clinical Resource Center - Call (847) 498-8364
Oct 24-26: Clinical Resource Center Presentations: Meaningful Use (Dr. Anitra Graves, FCCP), Coding and Reimbursement (Dr. Scott Manaker, FCCP), Negotiating Your First Contract (Dr. Michael Nelson, FCCP)
Oct 25, 10:15 AM – 11:15 AM: Coding and Billing Updates
Oct 26, 7:15 AM – 8:45 AM: The Changing Face of Health Care: Reimbursement, Financial Impact, and Trends
Oct 26, 10:15 AM – 11:15 AM: Accountable Care Organizations: Financial Rewards for Quality and Efficiency

Kim D. French, MHSA, CAPPM
NetWork Consultant

Respiratory Care

Resistance Measurements

For patients receiving mechanical ventilation, airway resistance (Raw) is the measure of the total resistance of the ventilator circuit, airway adapters, endotracheal/trach tube, and the patient's airways. Raw equals the change in pressure divided by flow: Resistance = Pressure/Flow. An electrical circuit analogy is Ohm's Law: Resistance = Voltage/Current.

The Pressure in cm H_2O is peak pressure minus plateau pressure. The Flow in liters per second (LPS) needs to be a square waveform and not a decelerating waveform. The units of

Continued on following page

This Month in *CHEST:* Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

EDITORIAL

- **A Unified Front Against COPD: Clinical Practice Guidelines From the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society, and the European Respiratory Society.** *By Dr. N. A. Hanania, FCCP; and Dr. D. D. Marciniuk, FCCP.*

POINT/COUNTERPOINT EDITORIAL

- **Efficacy of Bronchial Thermoplasty for Patients With Severe Asthma: Is There Sufficient Evidence?** *Yes. Dr. A. Shifren, FCCP, et al. Not Yet. Dr. G. Michaud, FCCP; and Dr. A. Ernst, FCCP.*

ORIGINAL RESEARCH

- **Oropharyngeal Aspiration and Silent Aspiration in Children.** *By Ms. K. A. Weir et al.*
- **Grading the Severity of Obstruction in Mixed Obstructive-Restrictive Lung Disease.** *By Dr. Z. S. Gardner et al.*
- **Increased Adverse Events After Percutaneous Coronary Intervention in Patients With COPD: Insights From the National Heart, Lung, and Blood Institute Dynamic Registry.** *By Dr. J. R. Enriquez et al.*

Continued from previous page

Raw are cm $H_2O/L/s^{-1}$, with normal values equal or below 10 cm $H_2O/L/s^{-1}$. LPM/60 converts to LPS, so a square flow waveform at 60 LPM equals 1 LPS. Raw calculations at Flow at 1 LPS simplify to Raw = Peak pressure – Plateau pressure. Raw is measured by the respiratory care practitioner noting peak pressure and then engaging the inspiratory hold momentarily to measure plateau pressure. If the ventilator offers an automated measurement of these pressures, confirmation should be performed using the graphics screen.

There are applications for Raw that could be integrated into hospital guidelines. Is bronchodilator therapy indicated? Baseline Raw should be elevated. What is the efficacy/duration of bronchodilator therapy? Efficacy: Raw should be lowered after treatment; duration: the time to re-elevation of Raw. Is there loss of patency of the endotracheal tube? Serial increases of Raw may be noted (Shah and Kollef. *Crit Care Med*. 2004;32[1]:120; Wilson et al. *Chest*. 2009;136[4]:1006.)

Dr. Herbert Patrick, MSEE, FCCP
NetWork Steering Committee Member

Thoracic Oncology

Cutting Edge Information Available at CHEST 2011

The publication of the National Lung Screening Trial (NLST) results in June 2011 remains the biggest news in lung cancer. The Thoracic Oncology NetWork congratulates NLST investigators, many of who were members of our NetWork, on this important achievement. This is the beginning, not the end, of efforts to reduce lung cancer mortality. Cost effectiveness data remain unpublished, and whatever these data show, we can clearly improve the cost effectiveness of early detection efforts by increasing our understanding of who is truly at risk for lung cancer. Biomarkers that inform us of the likelihood of lung cancer in screen-detected lung nodules are the next hurdle on which we will focus. A session on screening at CHEST 2011 will address these topics.

In addition to screening, numerous other recent advances in the lung cancer field are the subjects for sessions at CHEST in Honolulu. The field of targeted therapy has evolved more with identification of tumors with driving mutations susceptible to targeted agents such as crizotinib (ALK mutant tumors). A session on targeted therapies and individualized management of lung cancer will describe the rationale for use of these agents in lung cancer. In addition, sessions offered at CHEST include the following: Radiation From Medical Imaging, Management of Early-Stage Lung Cancer in High Risk Patients, Multimodality (Surgical) Treatment of Stage III Lung Cancer, and Quality of Care in Lung Cancer.

The Thoracic Oncology NetWork welcomes all interested individuals to our open meeting, Tuesday, October 25, at 7:15 AM.

Dr. Douglas Arenberg, FCCP
NetWork Chair

Transplant

Bioengineering Lungs for Transplantation

Lung transplantation, at one time, seemed like science fiction, but innovations in surgical technique and immunosuppression made it clinical reality. Limited supply of donor lungs and the vagaries of immunosuppression still limit its success.

A pair of articles published last year has created an aura of science fiction once again (Ott et al. *Nat Med*. 2010;16[8]:927; Petersen et al. *Science*. 2010;329[5991]:538). Two groups of researchers developed an engineered lung through decellularization and recellularization in a rat model. In the experiments, an explanted adult rat lung was decellularized with a detergent, creating a sort of scaffolding of the lung. It retained its ultrastructural properties with complete removal of antigenic cellular components. Preservation of lung architecture and microvasculature was seen on CT imaging. Even the alveolar septal architecture remained undisturbed.

This acellular matrix was mounted inside a biomimetic bioreactor, where fetal vascular endothelium could be seeded into the pulmonary artery and fetal pulmonary epithelium into the trachea. Inside the bioreactor, the lungs were perfused with blood and ventilated at physiologic pressures, with gas exchange comparable to native lungs under the same conditions. After 4 to 8 days of culture, the lungs were removed and successfully implanted into syngeneic rats where selective blood gas analysis demonstrated gas exchange in the engineered lungs.

Tissue-engineered lungs could alleviate donor availability and many of the allo-immunity problems, if such a concept could be developed to clinical reality. There are many hurdles to overcome, but along with other novel concepts, such as a microchip that performs gas exchange (*Science*. 2010 Jun 25; 328(5986):1662), we must wonder what the future holds for such technologies.

One of the lead researchers, Dr. Tom Peterson, will discuss the topic, "Tissue-Engineered Lungs for In Vivo Implantation" at the Transplant NetWork open meeting on Monday, October 24, at 7:15 AM in the Honolulu Convention Center, room 318B.

Dr. Daniel Dilling, FCCP
NetWork Steering Committee Member

Leadership Development and Mentorship

BY DR. SUHAIL RAOOF, FCCP
Incoming ACCP President

"Lives of great men all remind us, we can make our lives sublime, and, departing, leave behind us, footprints on the sands of time."
–Longfellow

One such indelible footprint has been left in the lives of many in the pulmonary/critical care community by Dr. Dorothy A. White, FCCP. She was a gifted clinician, a clear thinker, and a prolific writer who worked at Memorial Sloan-Kettering Cancer Center in New York. Living in New York, I had heard of her excellence and had read her scholarly papers on a vast array of subjects, especially on lung infections in immunocompromised hosts and chemotherapy-related pulmonary toxicity. Her colleagues, Drs. Neil Halpern and Diane Stover, describe her as an exceptional doctor who was able to extract a maze of information from the most complicated cases and distill from it what was relevant and important; she was the ultimate diagnostician. Above all, they spoke of a kind and gentle soul who was the consummate teacher, a person who taught her fellows artfully and supplemented their knowledge with her vast knowledge and body of experience. During all her years of mentoring, she was never demeaning or condescending to her junior colleagues. Unfortunately, she died in September 2010, but she left behind a legacy that will long be remembered.


DR. SUHAIL RAOOF, FCCP

Dr. Robert Lee is a young faculty member who joined the MSKCC team and took over Dr. White's patients (**see adjacent page**). His insights about her are very moving and touched hundreds of individuals who had gathered in homage of Dr. White. His first sentence, "I never met you, nor heard you speak…" attracted the attention of all. He talks about the profound impact Dorothy had on his life. She was his mentor "in absentia." She became a guiding star in his life, as he sought to emulate what she did or would have done in different situations.

Dr. Lee's words highlight the power of mentorship. Inspiring mentorship has the power to guide others to advance their careers and to develop to their full potential. Mentorship extends broadly to encompass values and virtues that a person may imbibe from a teacher or a colleague.

The ACCP is an institution that brings professionals together at different stages of their careers., Hence, it has the potential to instill an effective mentorship development process for the entire cross section of its membership.

In order for this process to have a meaningful impact on members, it should be multitiered. This is best exemplified by sharing some of the e-mails and conversations we have had this year from the following ACCP- and non-ACCP-associated people:

Students, Residents, and Fellows

Mr. Paul Markowski, ACCP's Executive Vice President and CEO, was approached by medical students, residents, and fellows at New York Methodist Hospital. Medical students requested that a link be set up on the College Web site to provide them with information, such as the spectrum of services covered under pulmonary medicine, the lifestyle, the usual pay scale, and the percentage of applicants who are accepted into pulmonary and critical care training programs. They sought the assistance of volunteer mentors from the College who could provide answers to their specific questions. Some medical students wanted to talk to physicians in academic and private practices and get a snapshot of "a day in their lives." One senior clinical fellow stated, "I am graduating in less than 1 year from my fellowship training. I aspire to become the President of the ACCP in 10 years. How can I get involved with the College from this stage onward, and how can the College help me to realize this dream?"

Recent Graduates From Fellowships and New FCCPs

A young physician in academic medicine had attempted to get involved with sleep networks of several societies, including the ACCP Sleep Medicine NetWork. After waiting around for several months, he became disappointed and almost resentful. He inferred that to get a break, he would need "someone from within the College to get him in." On occasion, senior members of the College saw their junior faculty members exhibiting exceptional dedication or expertise in their areas of work or interest. Such young faculty members hold the promise of the leaders of tomorrow. It is only appropriate that they be involved in the College from an early stage and be groomed for leadership roles for which they may demonstrate an aptitude.

General Membership and, Particularly, Those in Private Practice

As a College, it is our responsibility to inculcate leadership skills in our general membership. Such skills will equip our members to assume leadership positions in their hospitals and areas of influence. This aspect was clearly enunciated at our recent Board of Regents meeting.

Existing Leaders of the College

Another type of pressing need emerged in the summer months when nominations for ACCP leadership positions were being considered. Several members, selected for leadership roles, were unaware of what was expected of them. Their evaluations indicated delinquencies in participation in board meetings and conference calls. Their lack of involvement was perceived as lack of interest.
Hence, it was recommended, not surprisingly, that these individuals be replaced with others who demonstrate greater interest in College activities. Talking to some of these individuals revealed a very different story. Not having gone through a formal orientation for their committee assignments, they were not aware of what was expected of them. Not being acquainted with many of the individuals on their conference calls, and not being as well-versed as most with the issues being discussed, they did not announce their presence and were reluctant to actively participate in conference calls. As this is probably a common occurrence among our leadership, we need a solution to this type of quandary.

ACCP Staff and International Members

One ACCP international member, encouraged by his presentation of a "Case Puzzler" at CHEST 2010, wrote to us about his interest in getting involved in ACCP international leadership. "Please help me and guide me," he wrote.

And finally, since we have almost 90 staff members working at the College, many for much of their professional life, it behooves us to provide them with similar opportunities for leadership development at the College.

Plan of Action

For all the above reasons, the importance of launching leadership development within the College cannot be overemphasized. A supple ad hoc committee, consisting of young leaders of the College, physicians in private practice, a few ACCP Past Presidents, and staff, has been established. The group is chaired by Dr. Lisa Moores, FCCP.

This ad hoc committee considered the following action items:

- Setting up a mechanism whereby trainees and young faculty are aligned with senior faculty or mentors with similar professional or research interests.
- Exploring how to utilize the new IT capabilities of the College that are being put into place. With these expanded capabilities, the College can be in a better position to provide additional opportunities for those outside of existing leadership to get involved in the activities of the College and engage with one another.
- Implementing orientation courses for all new ACCP leaders each year. This may include an online component covering the structure, mission, and operations of the College, including general topics pertinent to leadership and governance, and a face-to face meeting specific to the committees on which that individual will serve.
- Designing an introductory and advanced leadership development course every year at CHEST, with an option to procure a "certificate of completion." An option to advance, annually, the skills acquired through these courses, needs to be developed. Programs and education will address the needs of different career levels. Targeted leadership development training will be provided for existing leaders at the spring governance meeting.
- Involving College leadership, including the Board of Regents, Membership Committee, Governors, Past Presidents, and NetWorks, to act as mentors for the junior ACCP members. Explore expanding opportunities for new FCCPs and members of the College to have roundtable conferences in open NetWork meetings and to interact with leadership at various functions during the annual meeting and other regional opportunities throughout the year.
- Requesting the International Governors and Regents to identify junior colleagues in their regions who possess leadership qualities and who may benefit from leadership development programs offered by the College. Such young international leaders may be considered for moderating sessions at CHEST and playing a meaningful role in the all-new "global" track, highlighting sessions with an international focus, at annual CHEST meetings.

The ad hoc committee has had a conference call, as well as a face-to-face meeting at ACCP headquarters in Northbrook, Illinois. It was gratifying to see the enthusiasm, experience, pragmatic approach, and desire to methodically implement this project in phases in a manner that will impact the culture of the College in a cogent and tangible way. We look forward to the committee's leadership role in this leadership development project. Dr. Darcy Marciniuk, incoming President-Elect, has also pledged to continue implementation of leadership development and mentorship in his year of presidency.

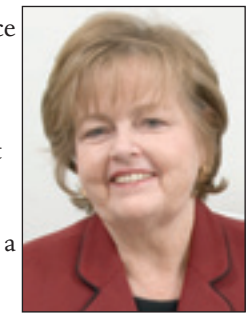
Thank you, Dr. White and Dr. Lee, for strengthening our resolve to launch leadership development and mentorship within our College. ■

Remembering Dr. Dorothy White, FCCP

BY DR. ROBERT P. LEE

Editor's Note: These insights were shared by Dr. Lee at the memorial service for Dr. Dorothy White, FCCP.

Looking back on how my medical career has progressed, I am fortunate to say that there has always been someone I can turn to for guidance and advice during every major step of the way. The reason I sought and heeded their advice was because of the tremendous respect I had toward them. These individuals earned my respect by teaching me not only through words, but by example, what it means to be a good physician. They helped me to set goals and pointed me toward the direction of where I needed to go. They are my mentors.


DR. WHITE

I would like share an unusual story of a special mentor in my life, who has impacted my recent career development. To give a little background information: I completed my training in pulmonary and critical care medicine, followed by a fellowship in interventional pulmonology in 2010. Then, I joined the faculty at Memorial Sloan-Kettering Cancer Center. Interestingly enough, as the most junior faculty member, I ended up filling the unexpected void of a prominent pulmonologist, Dr. Dorothy White. She unfortunately passed away a few months after I started. I had an opportunity to present the following letter at her Memorial Service:

Dear Dr. White,

I have never met you nor have I heard you speak. I don't know even the sound of your voice. Even if I had sat next to you on the subway or bus, I would not have known who you were. However, even in your absence, you have strongly influenced my life and my career, and I would like to take this opportunity to express my gratitude.

Shortly after your departure, my career began here at Memorial. I took over most of your patients, your office space, and even the same chair and computer in clinic. Just as you had before, I sit next to your nurse, Alice, and we work diligently together.

We have been extremely busy, but in the midst of the busyness, one of the interesting aspects in my day-to-day work, has been discovering more about who you were. You left your mark and essence in every corner, especially with your patients. Every single one of them speaks so highly of you, and they have some high expectations from me, as well! I think you may have set the standard a little too high. They describe you as kind and caring. Many say you were an extraordinary physician, and it was only after seeing you that their cough, shortness of breath, or other issues were finally resolved. Your patients describe the attributes of the kind of physician that I attain to be.

Many of your patients seemed to have a complicated and challenging clinical course when they saw you initially. It is through your detailed notes that I can see your flow of logic and the incredible clinical insight you had. I am learning much more than I had anticipated through this process. I recently evaluated a new patient with everolimus-related lung toxicity. It was actually my very first time encountering this, but I knew exactly what to do. I already had the benefit of learning from your other patients with the same pathology. From reading your notes, and caring for your patients, I receive the incredible transference of your vast knowledge and experience. Speaking of notes, you had a unique, almost artistic talent of summarizing the most complicated patient history into a concise paragraph. Needless to say, my patient recovered completely from the drug toxicity.

Your colleagues tell me how brilliant of a clinician you were. They say you were the "go to person" for any complicated pulmonary problems. That explains why I am learning so much from your patients. I sometimes feel as if you are present with me, teaching me and molding my thought process, like a mentor.

One day during rounds, as we were discussing an unusual case, I asked the fellows, WWDWD? To many puzzled faces I said, "I mean, What Would Dr. White Do? WWDWD?" It was a joke, of course, but it attests to the level of respect I have developed for you even only after a short time here at Memorial. As a matter of fact, I frequently find myself asking how you would have approached some of the complicated issues I have to deal with.

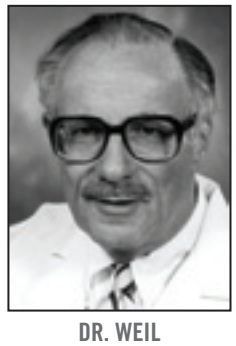
Thank you, Dr. White, for leaving me the privilege of your continued teaching, even after your departure. Thank you for setting the standard of excellence that I need to strive to attain. If anyone ever asks me who has influenced and shaped my career, I would undoubtedly include you, Dr. White, without hesitation, for you are my mentor, whom I never knew face to face.

I hope to convey and highlight the significance and importance of our work in the field of medicine. The work we do by caring for the sick, not only benefits the patients themselves but goes well beyond the four walls of the hospital room. Through the standards we set and the examples we display, we are, indeed, planting seeds for the future generations of physicians. These are the seeds that will eventually blossom and bear much fruit. The importance of mentorship in our medical education cannot be overemphasized. As practicing physicians, we have the power to influence the course of the future generations of physicians. ■

DR. LEE *is with the Memorial Sloan-Kettering Cancer Center.*

In Memoriam

Max Harry Weil, MD, PhD, Master FCCP, died on July 29, 2011, at his home in Rancho Mirage, California. Dr. Weil became a Fellow of the ACCP in 1975 and received the honor of Master Fellow in 1997. He served the College in several capacities, which included leadership roles in the Critical Care Institute and Critical Care NetWork and serving on the *CHEST* Editorial Board.


DR. WEIL

Dr. Weil received his medical degree from the State University of New York and completed training in cardiology and cardiovascular physiology at the Mayo Clinic in Rochester, Minnesota. His research focused on the mechanism of shock, the hemodynamic effects of endotoxin, and the relationship of endotoxic shock with other types of shock. In August of 1957, Dr. Weil opened the first center performing heart catheterization in California at City of Hope Medical Center in Duarte.

On the faculty of the University of Southern California from 1958 to 1981 and working first at Los Angeles County Hospital, and then at Hollywood Presbyterian Medical Center, he opened the Shock Research Unit, one of the first ICUs in the nation. He started the Institute of Critical Care Medicine in 1959 with Dr. Herbert Shubin in Los Angeles. He moved the Institute to a location in Palm Springs in 1991, and then to its current location in Rancho Mirage in 2005.

At the time of his death, Dr. Weil was still actively teaching cardiopulmonary resuscitation, designing research projects, and supervising the education of research fellows from around the world in the field of critical care and life support. Dr. Weil is often referred to as "The Father of Critical Care Medicine." ■

Information and photo kindly provided by The Weil Institute of Critical Care Medicine.

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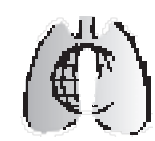

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FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

Diagnostic Coding Update for 2012: Interstitial Lung Diseases (ILD)

BY DR. ROBERT DEMARCO, FCCP, CHAIR; DONNA KNAPP BYBEE, MA, FACMPE, VICE-CHAIR; AND DIANE KRIER-MORROW, MBA, MPH, CCS-P, ACCP CODING AND REIMBURSEMENT CONSULTANT

Interstitial Lung Disease (ILD) is a broad term that covers over 100 individual disorders. These specific disorders are grouped together due to the similarities of their physiologic features, their clinical presentation, and their radiographic images. The tissue abnormalities that characterize most ILDs are in the interstitium and, eventually, affect a patient's ability to breathe. The patient's lungs also have more difficulty transferring oxygen to their blood streams. In most cases, the causes of ILDs are idiopathic (unknown). The disorders that are categorized as ILDs vary in diagnosis, treatment, and causality.

The ACCP Practice Management Committee, working with the American Thoracic Society Clinical Practice Committee, had requested several new 4th and 5th digit ICD-9-CM codes for several ILDs in order to increase specificity. These new ICD-9-CM codes in the Tabular List are listed in the Table. ILD codes are included in *Chapter 8: Diseases of Respiratory System (460-519)* of the ICD-9-CM book.

There are approximately 50 new ICD-9-CM codes all together that are of interest to pulmonary, critical care and sleep medicine, 15 of which are ILD codes. Of those ILD codes, 10 are new adult ILD codes ranging from **516.3** through **516.5** (some are four-digit codes and some are five digits). Two of these new four-digit adult ILD codes are for rare disorders. One is lymphangioleiomyomatosis (LAM), a fatal lung disease that affects women in childbearing years. The other is Pulmonary Langerhan's Cell Histiocytosis (PLCH), a smoking-related disease. The other eight adult ILDs are different types of idiopathic interstitial pneumonia. Dr. Frank McCormack, who presented the case for the new ILD codes to the National Center for Health Statistics Coordination and Maintenance Committee, said that "specific ILD codes will facilitate proper reimbursement, as well as clinical, epidemiology, and comparative effectiveness research." There are five new five-digit ILD codes for children that fall under **516.6** *Interstitial lung disease of childhood*.

Please ensure that you utilize these new codes starting on October 1, 2011, or your reimbursements will be denied. Also, be sure that your practice encounter forms, templates, and software are updated with these new codes. Official ICD-9-CM annual code revisions are referred to as addenda, and the first volume of the addenda index is available on the National Center for Health Statistics (NCHS) Web site at www.cdc.gov/nchs/data/icd9/ICD-9-CMINDEXAD DENDAfy12.pdf. The tabular list of diseases addenda (Volume II) can be viewed at www.cdc.gov/nchs/data/icd9/ICD-9-CM%20TABULAR ADDENDAfy12.pdf. When you check the source addenda, check both the Diagnoses Index and the Tabular List for selection of the appropriate codes to report. For example, in the new 54 codes of interest, the Index lists multiple pulmonary nodules. However, the code (793.19) referred to does not list multiple pulmonary nodules. These new ILD codes will also be transitioned to ICD-10-CM on October 1, 2013. ■

New ILD Diagnosis Codes From Tabular List

516 Other alveolar and parietoalveolar pneumonopathy
- **516.3** Idiopathic interstitial pneumonia
  - **516.30** Idiopathic interstitial pneumonia, not otherwise specified **(IIP)**
    Idiopathic fibrosing alveolitis
  - **516.31** Idiopathic pulmonary fibrosis **(IPF)**
    Cryptogenic fibrosing alveolitis
  - **516.32** Idiopathic non-specific interstitial pneumonitis **(NSIP)**
    Excludes: non-specific interstitial pneumonia NOS, or due to known underlying cause **(516.8)**
  - **516.33** Acute interstitial pneumonitis **(AIP)**
    Hamman Rich syndrome
    Excludes: pneumocystis pneumonia **(136.3)**
  - **516.34** Respiratory bronchiolitis interstitial lung disease **(RB-ILD)**
  - **516.35** Idiopathic lymphoid interstitial pneumonia **(LIP)**
    Idiopathic lymphocytic interstitial pneumonitis
    Excludes: lymphoid interstitial pneumonia NOS, or due to known underlying cause **(516.8)**, pneumocystis pneumonia **(136.3)**
  - **516.36** Cryptogenic organizing pneumonia **(COP)**
    Excludes: organizing pneumonia NOS, or due to known underlying cause (516.8)
  - **516.37** Desquamative interstitial pneumonia **(DIP)**
- **516.4** Lymphangioleiomyomatosis **(LAM)**
  Lymphangiomyomatosis
- **516.5** Adult pulmonary Langerhans cell histiocytosis **(PLCH)**
  Adult PLCH
- **516.6 Interstitial lung diseases of childhood**
  - **516.61** Neuroendocrine cell hyperplasia of infancy
  - **516.62** Pulmonary interstitial glycogenosis
  - **516.63** Surfactant mutations of the lung
  - **516.64** Alveolar capillary dysplasia with vein misalignment
  - **516.69** Other interstitial lung diseases of childhood
- **516.8** Other specified alveolar and parietoalveolar pneumonopathies
  Interstitial pneumonia
  Lymphoid interstitial pneumonia due to known underlying cause
  Lymphoid interstitial pneumonia NOS
  Non-specific interstitial pneumonia due to known underlying cause
  Non-specific interstitial pneumonia NOS
  Organizing pneumonia due to known underlying cause
  Organizing pneumonia NOS

Code first, if applicable, underlying cause of pneumonopathy, if known
Use additional E code, if applicable, for drug-induced or toxic pneumonopathy
Excludes: cryptogenic organizing pneumonia **(516.36)**
idiopathic lymphoid interstitial pneumonia **(516.35)**
idiopathic non-specific interstitial pneumonitis **(516.32)**

ACCP Media Update

The ACCP and the journal *CHEST* have garnered an array of news coverage in the past several months.

CHEST

▶ The *Indiana Gazette discussed a CHEST* study that found people admitted to intensive care units on weekends are more likely to die than those entering during the week.
▶ *The New York Times* featured a 2009 *CHEST* study about musicians developing respiratory infections after not washing their instrument mouthpieces.
▶ *The Dayton Daily News* and the *Journal News in Cincinnati* quoted ACCP Sleep Medicine NetWorks Chair Dr. Kenneth Casey, FCCP, in an article discussing how shift work affects sleep habits.
▶ *Sleep Review* and *RD Magazine* discussed a May 2011 *CHEST* study about how heart rates in children with obstructive sleep apnea syndrome change after having adenotonsillectomies.
▶ More than 10 years after it first appeared in *CHEST,* the "Chicken Soup" study still has legs. The 2000 *CHEST* study, which examined chicken soup as a remedy for the common cold, was featured in a July article, "Can Chicken Soup Cure a Cold?", which was used by ABC 22-TV in New York, Montreal, and Vermont, and by KXVO-TV in Nebraska.
▶ Additional *CHEST* studies have appeared in *Science Magazine, US Pharmacist, Nurse-Week, Contemporary OB/Gyn, Managed Care, KevinMD.com,* and *Rehabilitation Management*.

Guidelines

▶ COPD – Joint guidelines developed by ACCP, the American College of Physicians, American Thoracic Society, and the European Respiratory Society have appeared in a number of publications, including MedPage Today and the *St. Petersburg Times.*

COPD Alliance

▶ *Advance for Long-Term Care Management* featured the article "COPD Awareness: Get Residents Better Care, Diagnosis, and Treatment," which quoted JoEllen Wynne, MSN, FNP-BC, Vice Chair of the COPD Alliance, a collaboration between ACCP and four primary care medical associations. ■

PCCSU Lessons for September

▶ **Minimally Invasive Techniques for Diagnosing and Staging Lung Cancer.**
By Dr. Jonathan T. Puchalski

PCCSU
Pulmonary, Critical Care, Sleep Update

▶ **Noncystic Fibrosis Bronchiectasis.**
By Dr. Guang-Shing Cheng

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