Flu Pandemic Pushing Demand for ECMO

By Sherry Boschert
Elsevier Global Medical News

The anticipated demand for extracorporeal membrane oxygenation in the wake of pandemic influenza A(H1N1) threatens to overwhelm the facilities currently equipped with the technology. “In 5 or 10 years, every ICU will have this capability, and there are a thousand of those” in the United States, said Dr. Robert H. Bartlett, the first clinician to successfully use extracorporeal membrane oxygenation (ECMO) for adults with severe respiratory failure, in 1975. In the coming year, however, the 70-80 U.S. hospitals with ECMO capability could be swamped by patients with H1N1, despite the low lethality of this particular virus, because it is so widespread, he said.

Even if only a tiny portion of H1N1 patients get sick enough to need ECMO, “if 10 million patients get it, which is likely to happen, that’s more patients than all the existing ECMO centers could cope with currently,” said Dr. Bartlett, professor of surgery (emeritus), University of Michigan, Ann Arbor. He has been an adviser or consultant to at least 17 companies, many of which developed or market ECMO components. Initially developed to treat neonatal respiratory failure, ECMO uses cardiopulmonary bypass technology similar to that used for cardiac surgery, but it can be used for weeks rather than just a few hours. It provides gas exchange, allowing ventilator settings to be reduced and providing time for recovery or treatment of the underlying problem. The Extracorporeal Life Support Organization keeps a registry with results for approximately 40,000 U.S. patients of all ages who have received ECMO thus far, Dr. Bartlett said.

ECMO should be considered when an adult with respiratory failure has a 50% chance of dying, and is indicated if there is an 80% chance of dying, using conventional algorithms that take into account blood gas levels, ventilator pressure, the extent of shock, and other factors.

See ECMO • page 8

Study: Pandemic H1N1 Flu May Overwhelm ICUs

Canadian experience offers lessons.

By Robert Finn
Elsevier Global Medical News

Intensive care units could become overwhelmed if the pandemic influenza A(H1N1) virus spreads as widely as feared and progresses as rapidly as observed in a March-July 2009 outbreak in Canada, said Dr. Anand Kumar and colleagues in a study published online in the Journal of the American Medical Association and presented at a meeting of the European Society of Intensive Care Medicine in Vienna.

All beds in intensive care units in Winnipeg, Man., the site of the largest pandemic cohort, were occupied at the peak of the outbreak in June 2009, reported Dr. Kumar of St. Boniface General Hospital, Winnipeg. Among the 168 patients admitted to the ICU with confirmed or probable 2009 influenza A(H1N1), the average time from the onset of symptoms to hospitalization was 4 days, and the average time from hospitalization to ICU admission was 1 day. The average age of these patients was 32.3 years; 67% were female, and 30% were children. The findings were based on prospective and retrospective data from 18 adult and pediatric intensive care units in Canada.

See Pandemic • page 9

Surgery Options Weighed in Early NSCLC

By Jeff Evans
Elsevier Global Medical News

Segmentectomy could be the procedure of choice for preserving lung function in patients with peripheral stage I A non–small cell lung cancer if indeed it can provide the same rate of disease-free survival as lobectomy.

A randomized trial currently underway should help to address some of the surgical community’s concerns about the size and conduct of the previous randomized trial that made lobectomy the surgical standard of care for most patients with early, node-negative, non–small cell lung cancer (NSCLC), said Dr. Nasser K. Altorki, FCCP, one of the study chairs for the current trial.

The earlier trial of 247 patients by the Lung Cancer Study Group (LCSG) showed that lobectomy resulted in a significantly lower rate of locoregional recurrence than did segmentectomy or wedge resection. (Locoregional recurrence was a secondary end point.) There also were no

See NSCLC • page 18

Sleep Institute
American College of Chest Physicians

Sleep Strategies
What's driving the success of the ABSM board exam?
See page 10.
Lung Function Preserved With New Inhaled Insulin

BY MIRIAM E. TUCKER
Elsavser Global Medical News

VIENNA — Technosphere inhaled insulin therapy maintained effective glycemic control with only small changes in lung function for at least 4 years in a study of 229 patients with type 2 diabetes. Technosphere insulin (TI) is an inhalation powder being developed by the MannKind Corporation as part of a drug-device combination product along with an inhaler. The company has submitted a new drug application to the Food and Drug Administration for approval of the product (Afrezza) for the control of hyperglycemia in adults with type 1 or type 2 diabetes.

The insulin comes in premetered single-use dose cartridges placed into the inhaler. When administered at the start of a meal, the TI dissolves and reaches the bloodstream rapidly, approximating the release of mealtime insulin in nondiabetic individuals. Peak plasma concentrations of 30 units of TI are reached within 10 minutes, compared with 45-60 minutes for 10 units of injected lispro insulin, Dr. Nikhil Amin said at the annual meeting of the European Association for the Study of Diabetes.

In all, Afresa phase II/III clinical trials have included more than 4,500 adult patients and have shown dose-related improvements in hemoglobin A1c, as well as safety with up to 2 years’ follow-up, said Dr. Amin, medical director, pulmonary, at MannKind Corp., Paramount, N.J.

He presented data from an open-label, multicenter, uncontrolled extension study of patients who had previously completed one of two 3-month placebo-controlled, randomized phase II studies. Technosphere was given 2-4 times a day at meals, with doses titrated according to the blood glucose in 15-unit increments.

Fifty-nine percent of the 229 patients were male, with a mean age of 56 years. Their overall mean exposure time to TI was 30 months, with 26% having more than 36 months of exposure and 14% having more than 42-48 months of exposure. A total of 69 patients (30%) discontinued study. The primary reason was the patient withdrawing consent (12%). Adverse events accounted for 7% of discontinuations, Dr. Amin said.

The primary end point was change in pulmonary function tests. Forced expiratory volume in 1 second (FEV1) did not change significantly over time, with nearly identical means of 2.99 L at baseline and 2.96 L at 48 months. Similarly, forced vital capacity (FVC) was 3.85 L at baseline and 4.14 L at 48 months, with little variability over time. Lung diffusion capacity (DLco) was 25.6 mL/min per mm Hg at baseline and 26.16 mL/min per mm Hg at 48 months.

The annual rates of change for each of the three measures over 4 years among the TI study group were similar to those reported in the literature for patients with type 2 diabetes in general. The mean FEV1 decline was of 0.048 L/year with TI, compared with 0.061 L/year reported for the general population of patients with type 2 diabetes. The drop in mean FVC was 0.058 L/year vs. 0.060 L/year for the general type 2 diabetic population, while mean DLco declined by 0.332 mL/min per year with TI, compared with 0.385 mL/min per year, he reported.

Mean Hb A1c levels were 7.97% at baseline and remained steady with a slight decline through month 48, down to 6.45%

Adverse events were reported by a total of 84% of the study group, and serious events by 13%. Adverse events leading to discontinuation occurred in 7%. The most common adverse events (excluding hypoglycemia) were cough (28%), upper respiratory tract infection (17.5%), nasopharyngitis (14%), arthralgia (8%), and back pain (8%). If approved, Afresa would follow in the footsteps of Pfizer’s inhaled insulin product Exubera, which was pulled from the U.S. market in 2007 after just over a year due to poor sales.

Dr. Philip Marcus, MPH, FCCP, comments: Inhaled insulin in the form of Exubera was to provide a viable alternative to frequent insulin injections. However, due to concerns about pulmonary damage and a device that did not seem to be user friendly, sales did not “take off” as expected. Perhaps Technosphere insulin will fill the void. The data on lung function over time look promising. The actual device also will have a lot to do with the success of the product, if approved, because the majority of people using it will have no prior experience with inhalers.

WHO: Treat Severe H1N1 Flu With Antivirals

BY JONATHAN GARDNER
Elsavser Global Medical News

Physicians should use oseltamivir to treat patients with severe or progressive cases of infection with the pandemic influenza A(H1N1) virus. If that drug is unavailable or if the virus demonstrates resistance to it, treat with zanamivir, indicated for treatment of flu viruses, applies to all chronic care—should be treated with one of these agents if they have mild to moderate uncomplicated clinical presentations. Physicians need not prescribe antivirals for asymptomatic individuals (those deemed not “at-risk”) who have mild to moderate cases of the infection. Where the risk of complications from infections is high—either due to the virus strain or the baseline risk of the exposed group—the drugs might be used as post-exposure chemoprophylaxis for at-risk individuals and for health care workers. If the complication risk is low, chemoprophylaxis need not be offered to these groups.

The guidelines represent the consensus of an international panel evaluating evidence on the use of antivirals in a pandemic, including treatment of the pandemic H1N1 virus circulating globally. It follows initial recommendations made in May.

©Copyright 2009, by the American College of Chest Physicians

CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for CHEST PHYSICIAN is provided by International Medical News Group and Elsevier Global Medical News. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians. The opinions and statements expressed in CHEST PHYSICIAN do not necessarily reflect those of the American College of Chest Physicians, or of its officers, agents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, agents, members, and employees, and Elsevier Inc. do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

Address Changes: Fax changes of address (with old mailing label) to CHEST PHYSICIAN, 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960.

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

CHEST PHYSICIAN is indexed in Index Medicus/Medline.

EDITORIAL ADVISORY BOARD
Doreen Addizzo-Harris, M.D., FCCP, New York
W. Michael Alberts, M.D., FCCP, Florida
Richard Fisher, M.D., FCCP, California
Stephen A. Geraci, M.D., FCCP, Mississippi
Nicola A. Hanania, M.D., FCCP, Texas
Burt Levinson, M.D., FCCP, Georgia
Philip Marcus, M.D., MPH, FCCP, New York
Mark L. Williams, M.D., FCCP, Connecticut
Stephen M. Pastores, M.D., FCCP, New York
Nirupam Singh, M.D., California
Keith W. Willis, M.D., FCCP, Alabama

E-mail: chestphysician@news@chestnet.org

©Copyright 2009, by the American College of Chest Physicians

CHEST PHYSICIAN
ELSEVIER SOCIETY GROUP, A DIVISION OF INTERNATIONAL MEDICAL NEWS GROUP
President, INMG Alan J. Incracht
Executive Director, ENMG Mark Branca
Editor in Chief, ESNG Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck
Managing Editor, ESNG Rhys
Deputy Managing Editor, ESNG Jay C. Cerniak

Circulation Analyst Barbara Cavallo, 973-290-8253, b.cavallo@elsevier.com
Executive Director, Operations Jim Chicca
Director, Production and Manufacturing Yvonne Evans
Production Manager, Jodi Shaffer
Creative Director, Louise A. Koenig

Display Advertising Manager: The Walchli Tauber Group: 443-512-8899, fax 443-512-8895, greg.passaglia@wgtigroup.com

ADVERTISING OFFICES
60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8250, fax 973-290-8250

CLASSIFIED ADVERTISING OFFICES
The Walchli Tauber Group, 2225 Old Emmorton Rd., Suite 201, Bel Air, MD 21015, 443-512-8899

EDITORIAL OFFICES
6363 Fishers Lane, Suite 6000, Rockville, MD 20852, 240-221-4500, fax 240-221-2541

DITRIONL
CHEST PHYSICIAN
NOVEMBER 2009 • CHEST PHYSICIAN
LungPoint™
First in Virtual Bronchoscopic Navigation

LungPoint Virtual Bronchoscopic Navigation uses the power of CT imaging and advanced software algorithms to help you navigate through the lung airways quickly and accurately.

This next-generation Virtual Bronchoscopic Navigation offers multiple advantages over early Electromagnetic Navigation systems that rely on proprietary hardware and disposable catheters, which means better bronchoscopy for you and a superior return on investment for your hospital!

For more information: 877.428.1600 or sales@broncus.com
www.broncus.com
### Changes Coming to Lung Cancer Symptom Survey

The survey’s four new measures will be independence, sleep, anxiety, and depression.

**By Robert Finn**
Elsevier Global Medical News

San Francisco — A Web-based survey of 660 patients with lung cancer will result in four new items being added to a widely used quality of life measure, according to a report at the World Conference on Lung Cancer.

The Lung Cancer Symptom Survey (LCSS) will be changed for the first time in 20 years, said Dr. Richard J. Gralla, who led the study. The four new items are independence, sleep, anxiety, and depression.

Intended to improve the content validity of LCSS, the anonymous survey was conducted among patients with lung cancer who registered with NexCura Inc., a company that provides Web-based tools to assist patients, caregivers, and providers in making evidence-based decisions. It was posted for 1 week in mid-2007 at www.nexcura.com, and was completed by 660 people.

A part of Thomson Reuters’s Thomson Scientific & Healthcare marketing group, NexCura also offers market research services. Dr. Gralla, chief of hematology and oncology at North Shore University Hospital in Manhasset, N.Y., and Long Island Jewish Medical Center in New Hyde Park, N.Y., is a member of NexCura’s medical editorial board.

The respondents’ median age was 62 years, 55% were female, and 77% reported having non-small cell lung cancer. In all, 25% of the patients reported having metastatic (stage IV) disease, 35% reported locally advanced (stage III) disease, 34% said they had no current evidence of disease, and 6% said they didn’t know the extent of their disease.

At the time of the survey, 63% had received their diagnosis less than 1 year previously, 24% received it 1–2 years previously, and the remaining 13% had survived more than 2 years since their diagnosis.

Patients were asked to rank 20 factors on a 5-point scale ranging from “most important” to “not important at all.” The top five factors rated as very important or most important were quality of life (80% of patients), independence (71%), not being a burden to others (67%), ability to perform normal activities (64%), and ability to sleep (63%).

“We were surprised that the top five items were not symptoms of lung cancer,” Dr. Gralla said. “They’re more global issues, and the symptoms come in a little bit lower” on the scale.

The next five factors were pain (59%), fatigue (58%), shortness of breath (58%), hemoptysis (58%), and depression (47%).

At the bottom of the scale were sexual difficulties (20% of patients ranking this as very important or most important), hoarseness (27%), problems with urination (27%), cough (28%), and meaning of life (32%).

With two exceptions, patients with metastatic disease ranked the factors similarly to those with no evidence of disease. Dr. Gralla said, “The two notable exceptions were pain—those with metastatic disease took the Nova item from the whole group and raised it to the third most important item, (whereas) those with no evidence of disease had it go down to nine—[and] hemoptysis remained a not very important item (No. 9) for those with metastatic disease, but was raised up higher [ranking sixth] for those with no evidence of disease.”

Dr. Gralla acknowledged that the Web-based survey had a number of limitations. For example, patients had to have access to a computer and some degree of computer literacy. They had to have enough interest in their disease to go online for information and to complete a survey form. And, as with all such surveys, patients who were very ill were less able to participate.

Nevertheless, the changes in the LCSS resulting from the survey are likely to be influential. “This hopefully will have some influence on how the [Food and Drug Administration] looks at evaluation of new drugs,” Dr. Gralla said at the meeting, which was sponsored by the International Association for the Study of Lung Cancer.

Dr. Gralla stated that he serves as an adviser on lung cancer to NexCura, and two of the four authors of the study are NexCura employees. The study received no specific funding.

---

### Heart Failure Patients Need Better Influenza Protection

**By Diana Mahoney**
Elsevier Global Medical News

Boston — Patients with heart failure do not maintain protective levels of antibody titers following influenza vaccination, leaving them already at-risk populations even more vulnerable to influenza-related complications, according to a study presented at the annual scientific meeting of the Heart Failure Society of America.

To determine whether heart failure patients sustain postvaccination influenza seroprotection throughout the flu season, Orly Vardeny, PharmD, of the University of Wisconsin at Madison, and colleagues evaluated 62 heart failure patients (median age 57) and 40 healthy controls (median age 49) during the 2006-2007 and 2007-2008 influenza seasons. The investigators measured serum antibody production via hemagglutination inhibition assay before influenza vaccination and 2–4 weeks and 6 months after vaccination, and compared antibody titers to individual vaccine viral strains after flu season to measure the persistence of antibody response.

All of the participants showed early antibody seroprotection, defined as postvaccination hemagglutination inhibition (HAI) antibody titer greater of at least 40, with similar rates of seroconversion between the heart failure patients and the healthy controls. Antibody titers decreased over time in both groups throughout the influenza season, said Dr. Vardeny. But the decreases observed among the healthy controls did not drop below the threshold of protective levels, whereas those observed in the heart failure patients did, “which made the heart failure patients more susceptible to influenza,” she said.

Specifically, titer levels to the A(H1N2) viral strain fell from a peak of 320 to 60 post season in the healthy controls and from 160 to 10 in the heart failure patients, and titer levels to the A(H1N1) strain fell from 160 to 80 in the healthy controls and from 60 to 30 in the heart failure patients, Dr. Vardeny reported. Titers to the less virulent B-type strain fell similarly in both groups, she noted.

In a study published earlier this year, Dr. Vardeny and her colleagues identified differences in immune responses to influenza vaccination in heart failure patients compared to healthy controls. Patients determined that patients with heart failure had higher vaccine-induced interleukin 10 concentrations, suggesting a different cytokine profile, and a different phenotype for vaccine responses, and that heart failure patients maintained a less vigorous antibody immune response to the newest vaccine viral strain than did the healthy controls (J. Card. Fail. 2009;15:368-73).

The findings may help explain the observed efficacy in heart failure patients of the vaccine targeting the more powerful influenza A strain, and they highlight the need for a solution, said Dr. Vardeny. “It’s clear that people with heart failure, who are already at risk for influenza-related complications, need better protection against influenza,” she said. Poor and suboptimal protective antibody titers should be considered included higher doses of the vaccine, which might offer season-long seroprotection, or mid-season boosters, she added.

Dr. Vardeny reported no financial relationships to disclose.

---

CPT Codes Designated For H1N1 Vaccination

**By Heidi Splete**
Elsevier Global Medical News

The American Medical Association has created a new Current Procedural Terminology (CPT) code (90670) and revised an existing code (90663) for use with H1N1 vaccinations, according to a statement issued Sept. 29 by the association.

The new and revised CPT codes will help streamline vaccination reporting and reimbursement as physicians across the United States prepare to administer nearly 200 million doses of the new H1N1 vaccine this fall, the AMA said in the statement.

The details of the codes are as follows:

- **90470**: H1N1 immunization, both intramuscular and intranasal, including counseling.
- **90663**: Influenza virus vaccine (pandemic H1N1 formulation).
- **90670**: Both the new Category I CPT Code 90470 and the revised code 90663 are effective immediately. Code 90470 was created for use when reporting H1N1 vaccine administered, while code 90663 was revised to include the specific H1N1 vaccine product, according to the statement.

To be paid for H1N1 vaccine administration, providers should bill 90663 in conjunction with 90470, the AMA said.

The 90663 code should be billed at zero dollars, because the vaccine itself is being provided by the federal government for no charge. Providers will be paid for vaccine administration, the AMA said.

The codes were created in a joint effort between the AMA CPT editorial panel and the U.S. Department of Health and Human Services.

Dr. Philip Marcus, MPH, FCCP, comments: The CPT process has worked quickly to provide the appropriate codes needed to secure reimbursement for administration of the H1N1 influenza vaccine. Of course, there will be no reimbursement for the vaccine itself, as it is being provided at no cost to physicians. In addition, there has been a revision in ICD-9 codes to reflect infection with the H1N1 virus, should it occur, and hopefully not in patients appropriately immunized.
WellPoint Alters Asthma

WellPoint heard that members did not like inhaled treatments or were struggling to take them.

BY GREGORY TWACHTMAN

“The Pink Sheet”

The WellPoint health plan has lifted the rules that require prior authorization for oral asthma medications, based on a comparative effectiveness analysis of claims data for oral and inhaled asthma medications.

Despite inhaled drugs’ clinical superiority in controlled trials, they have been underutilized or discontinued by HealthCore (WellPoint’s health outcomes research subsidiary), revealed that users of oral asthma controllers appeared to have better clinical outcomes than did the inhaled corticosteroid (ICS) group, as indicated by less use of short-acting beta-agonists and a smaller risk of inpatient and emergency department visits, according to the authors of an analysis published in the August 2009 edition of Mayo Clinic Proceedings.

The study came about, according to WellPoint’s National Pharmacy and Therapeutics Committee, when it found that oral asthma medications were being used as front-line therapy, a use that either wasn’t part of the drug’s FDA-approved indication or didn’t follow the National Heart, Lung, and Blood Institute’s asthma treatment guidelines.

WellPoint said it was hearing anecdotal evidence that members did not like inhaled treatments or were struggling to take them, prompting the insurer to find out “which therapy was best for members in the real world and align our formulary appropriately.”

For the study, HealthCore examined the medical and pharmacy claims of more than 55,000 patients from eight health plans who had used at least one of six types of asthma controller medications between 2003 and 2005. The data were integrated with quality of life survey results of more than 800 asthma patients from the same plans to evaluate potential differences in quality of life between the types of controller medication. The oral medications that patients in the study were using were the leukotriene modifiers zafirlukast (Accolate), montelukast (Singulair), and zileuton (Zyflo).

Lead author Hangkiti Tan and colleagues suggested that the reason for the better outcomes among the oral medication users comes down to real-world usage patterns.

Drug Benefit After Study

“This conflict could be due to the observation that the patients in this study were less adherent to an inhaled controller medication (inhaled corticosteroid, long-acting beta-agonist) regimen than to an oral controller medication regimen,” the authors suggested. “This observation concurred with the findings of other studies, which indicated that adherence was poorer for inhaled medications, both in general and in comparison with oral medications” (Mayo Clin. Proc. 2009;84:675-84).

In a statement, WellPoint said its National Pharmaceutical and Therapeutics Committee “chose to keep the oral controller used by the vast majority of its members on the same formulary tier and lift its prior authorization requirement.”

“Only 3% of patients in the ICS group were considered adherent, a finding that underlines the urgent need for a better understanding of the barriers to patient acceptance of the most proven and effective therapy,” the researchers added. “When ICS adherence cannot be achieved, our findings indicate that a [leukotriene modifier] may be a reasonable alternative.”

The study’s authors noted that among patients who adhered to their controller medication regimen, the risk of inpatient or emergency department visits was lower for patients receiving an ICS than for those taking an oral medication.

But the findings underscore a recurring theme in discussions regarding comparative effectiveness research: just how an intervention is used in the real-world setting can differ from the way it is used in the clinical trials that are designed to determine a drug’s safety and efficacy. Recognizing that the Federal Coordinating Council for Comparative Effectiveness Research recently finalized its definition of comparative effectiveness, placing an emphasis on comparing interventions in “real-world” settings.

This newspaper and “The Pink Sheet” are published by Elsevier.

Dr. Philip Marcus, MPH, FCPP, comments: Asthma guidelines, recently updated in August 2007, indicate that inhaled corticosteroids are the preferred therapeutic option for maintenance therapy of persistent asthma. The use of leukotriene-modifying drugs is an alternative, but not a preferred option for maintenance therapy. The findings in this study show the difference between efficacy, as noted in clinical trials, and effectiveness, as noted in “real-world” settings. The decision to allow the nonpreferred alternative therapies offers patients an option they find more acceptable, although the outcomes may be less optimal. Perhaps something is better than nothing.”
RSV in Young Children Linked to Heart Damage

BY ROBERT FINN

SAN FRANCISCO — Respiratory syncytial virus itself, and not the bronchiolitis associated with the infection, appears to be the cause of the heart damage often seen in young children with the virus, according to a prospective study involving 74 children.

All 74 children were less than 12 months of age and were admitted to the hospital for bronchiolitis. Dr. Susanna Espostio explained in a poster at the Interscience Conference on Antimicrobial Agents and Chemotherapy. Aside from their bronchiolitis, the children were healthy. Investigators excluded children from the study if they had a chronic disease that increased the risk of complications of a respiratory infection.

The investigators from the University of Milan collected specimens with nasopharyngeal swabs to detect respiratory syncytial virus (RSV) types A and B. A careful heart evaluation has to be performed in all the children with RSV bronchiolitis,“ the investigators wrote. “A careful heart evaluation has to be performed in all the children with RSV bronchiolitis.”

The investigators reported that they had conflicts of interest.

Study Will Test H1N1 Flu Vaccine in Pediatric Asthma

BY MICHELE G. SULLIVAN

A new phase II trial will test the safety and efficacy of the pandemic influenza A(H1N1) vaccine on patients with mild, moderate, and severe asthma. Although the vaccine has already been approved as safe and effective in the general population, additional studies are necessary to confirm its effect on those with asthma—especially those who take glucocorticoid medications, Dr. Anthony Fauci said in a statement.

“We need to determine the optimal dose... that can be safely administered to this at-risk population.”

The study, sponsored by NIAID and the National Heart, Lung, and Blood Institute, plans to enroll 150-400 healthy subjects aged 12 years and older with mild, moderate, or severe asthma. Participants will be stratified into two groups: those with mild to moderate versus those with severe asthma. All participants will be randomly assigned to receive either a high dose (30 mcg) or low-dose (15 mcg) H1N1 vaccine. Both vaccine dosages will be administered in two intramuscular injections 21 days apart.

Reduced Bone Mineral Density, Low Vitamin D Seen in CF Patients

BY DOUG BRUNK

SAN DIEGO — Reduced bone mineral density is common in children with cystic fibrosis, and few have normal serum concentrations of vitamin D, based on the results of a multicenter, cross-sectional study of 100 children with cystic fibrosis.

“The most important factors influencing bone mineral density are glucocorticoid use, poor nutrition, hypogonadism, physical inactivity, and malabsorption of vitamin D,” but the exact pathogenesis of low bone mineral density in patients with cystic fibrosis is still unclear,” said lead investigator Dr. Dorota Sands of the department of pediatrics at the Institute of Mother and Child, Warsaw, Poland.

“However, nutritional factors probably play a major role.”

The average age of the patients (51 boys and 49 girls) was 13 years, and all had severe pancreatic insufficiency and were compliant with vitamin supplementation. All patients were asked to complete a 3-day dietary questionnaire and underwent standard biochemical blood tests and bone mineral density (BMD) testing with dual-energy x-ray absorptiometry. Dr. Sands reported in a poster session at the annual meeting of the Society for Inherited Metabolic Disorders.

Results of the cross-sectional component of the study revealed that 55 patients had a BMD within the normal range and 45 had a z score of –1 or below.

The researchers reported that 65% of the patients had normal nutritional status and that their mean values of calcium and phosphorus blood concentrations were within normal limits.

Although the mean serum 25-hydroxyvitamin D (25(OH)D) levels were within normal limits, 21% had high levels of parathyroid hormone, and 77% had osteocalcin levels that exceeded normal limits.

“Only 12% had a sufficient dietetic supply of vitamin D,” Dr. Sands added. “Dietetic supply of vitamin D was on a low level, providing on average only 37% of the Recommended Daily Allowance (RDA); 55% of patients did not achieve the RDA for calcium intake.”

A longitudinal analysis was performed in the 45 study participants who had a z score of –1 or below. These patients received an intervention consisting of 0.25 mcg of vitamin D3 for 1 year. After 1 year of treatment with vitamin D3, the mean z scores were –1.87, and in 51% of patients, the z scores worsened.

Nearly three-quarters of patients (70%) did not achieve the RDA for calcium intake, and the mean values of calcium and phosphorus blood concentration remained within normal limits.

The study was supported by the Nutricia Research Foundation.
ECMO Improved Survival in H1N1-Induced ARDS

THE INCIDENCE OF ARDS SUITABLE TO WARRANT CONSIDERATION OF ECMO … EXCEEDS 2.6 PER MILLION INHABITANTS.

Most patients in Australia and New Zealand who developed acute respiratory distress syndrome due to 2009 influenza A(H1N1) and were treated with extracorporeal membrane oxygenation survived, with a mortality rate of 21%. The results were drawn from data compiled during the winter season in these countries.

“Despite the disease severity and the intensity of treatment, the mortality rate was low,” Dr. Andrew R. Davies of Monash University, Melbourne, and his colleagues reported online in the Journal of the American Medical Association.

“Our findings have implications for health care planning and the clinical management of patients with 2009 influenza A(H1N1) during the 2009-2010 northern hemisphere winter. Our results indicate that the incidence of ARDS [acute respiratory distress syndrome] sufficient to warrant consideration of ECMO … exceeds 2.6 per million inhabitants.”

A total of 252 patients were admitted to participating ICUs for the combination of respiratory failure (4) were the most common causes of death. Notably, 7 of the 10 pregnant/postpartum patients survived. All three of the children treated with ECMO were alive, though one was still in the ICU.

During ECMO, hemorrhagic complications occurred in 64% of patients and infective complications in 62%.

The researchers estimated the incidence of ECMO use for the combination of confirmed and suspected 2009 influenza (A(H1N1)) during the winter season to be 2.6 cases per million people. When only confirmed cases were considered, the incidence fell slightly to 2.0 cases per million. By comparison, 0.15 cases per million were treated with ECMO for ARDS in the preceding winter season.

The investigators also obtained data on 133 patients with confirmed H1N1 infection in the same ICUs who were treated with mechanical ventilation but not ECMO. Patients treated with ECMO had longer median durations of mechanical ventilation (18 days vs. 8 days), longer median ICU stays (22 vs. 12), and greater ICU mortality (14 vs. 12), compared with those who did not receive ECMO.

Dr. Davies treats patients in the ICU of Alfred Hospital in Melbourne. The authors reported that they have no relevant financial relationships.
Optimal Use of ECMO Debated

ECMO • from page 1

Survival rates for patients with severe respiratory failure can approach 60%–70% if ECMO is used early on, according to Dr. Bartlett. In the current cost of ECMO is approximately $2,000/day, but that will drop as the newer technology becomes more widely adopted, he added. In fact, advances in technology in the past few years have made ECMO simpler and less expensive to use, according to Bartlett.

In a multicenter, randomized, controlled trial involving 446 patients (103 patients were assigned to ECMO and 343 were assigned to usual care) at 29 centers in Germany, France, Netherlands, Italy, and Spain, ECMO was associated with a significantly higher rate of survival in patients with refractory respiratory failure secondary to acute respiratory distress syndrome (ARDS) (18.3% vs. 13.9%).

The investigators, led by Dr. Thomas Lichtenstein of the University of Heidelberg in Germany, concluded that the higher survival rate seen in the ECMO group over the control group was likely due to a lower rate of death from sepsis in the ECMO group (17.1% vs. 23.3%) and fewer patients requiring mechanical ventilation, which has been associated with higher mortality.

The finding also supports the use of ECMO in the treatment of refractory respiratory failure, especially in patients with severe ARDS, but “that’s a lot more Continued on following page”
Canadian ICUs Grapple With Flu Pandemic • from page 1

Infection increases with the upcoming flu season, there will be an acutely increased demand for ICU care, including the need for rescue therapies that are not currently widely available. Clinicians and policy makers will need to examine feasible methods to optimally expand and deploy ICU resources to meet this need,” the researchers wrote.

In an accompanying editorial, Dr. Douglas B. White and Dr. Derek C. Angus of the University of Pittsburgh noted that many hospitals in the United States may not have enough physicians with expertise in the needed rescue therapies, and even those hospitals with expert physicians may not have the staffing structures in place that would allow timely treatment 24 hours a day (JAMA 2009. Oct. 12 [doi:10.1001/jama.2009.1539]).

Dr. White and Dr. Angus proposed that care could be regionalized, with a few hospitals accumulating experience managing the sickest patients.

Telemedicine consultations between experts and physicians at outlying hospitals might help. In addition, hospitals could make temporary staffing changes.

“Hospitals must develop explicit policies to equitably determine who will and will not receive life-support efforts,” he said.

Continued from previous page

controversial” than providing ECMO to allow recovery, he said. Dr. Hoopes reported having no conflicts of interest related to these topics.

“We have been impressed in the last 6 months how many people with presumed H1N1 influenza we’ve heard about or gotten calls from,” he said. Discussions are underway at many ECMO centers to reach some consensus on criteria for referring patients. The key, Dr. Hoopes said, is to call the ECMO center sooner rather than later, to at least begin discussions.

“Let us know up front if someone has been on the vent for 5 days, is young, and is going in the wrong direction,” he said. If you wait to use ECMO in a last-ditch salvage attempt, as has often been the case, half of the patients will die.

The numbers aren’t yet available on survival rates with earlier use of ECMO in patients with respiratory failure from presumed H1N1 influenza, “but they’re definitely better than if you wait until it’s salvage,” Dr. Hoopes added.
NEWS FROM THE COLLEGE

SLEEP STRATEGIES

BY DR. BARBARA PHILLIPS, FCCP
Sleep Institute Co-Chair

AND JOHN STANGEL, CCMEP
ACCP Manager of Enduring Products

In late August, the ACCP offered the 4th Sleep Medicine Board Review Course in conjunction with its time-honored and popular critical care and sleep medicine board review courses. An astounding 800 individuals registered and attended the 4-day course in Phoenix, AZ. (This is not quite a record; Mr. Al Lever (personal communication, August 21, 2009) reported that more than 1,000 individuals took the ACCPs board review course for critical care when the first critical care certifying examination was offered.)

How Did This Happen, and Who Are These People?
Both training (eg, fellowship and postgraduate training) and credentialing (board certification) in sleep medicine have evolved rapidly in the last several years. The American Board of Sleep Medicine (ABSM) began as arogue board, not recognized by the American Board of Medical Specialties (ABMS). Initially, the ABMS was managed by the American Academy of Sleep Medicine (AASM), which successfully sought ABMS recognition. The new ABMS-recognized Sleep Medicine Board is housed in the American Board of Internal Medicine (ABIM) and is conjoinedly administered by the ABIM, the American Board of Psychiatry and Neurology, The American Board of Otolaryngology, and the American Board of Pediatrics and the American Board of Family Medicine.

The first ABIM-sponsored sleep medicine board examination took place on November 13, 2007. A total of 1,880 people took the exam, and the overall pass rate was 73%. As one would predict, those with previous board certification by the ABMS had a high pass rate of 93%, while those who did not undergo any formal training and registered for the test via the self-attestation pathway, did not fare as well, with an overall pass rate of only 59%.

It is the ABMS’s policy that ALL new board examinations under its umbrella must offer a 5-year grandfather period. Thus, clinicians who have been practicing in that field are eligible to take the new examination if they have a significant amount of experience in the medical practice of sleep medicine. In other words, people who choose to become board-certified in sleep medicine but have not yet been able to do so are eligible to take the new ABMS-recognized examination (which is only offered every other year) through the 2011 exam. This and the upcoming Centers for Medicare & Medicaid Services (CMS) changes regarding reimbursement for sleep study interpretation likely explain the popularity of the board review course.

Who Is Taking the ABSM Sleep Medicine Board Exam?

An astounding 800 individuals attended the ACCP Sleep Medicine Board Review Course. This information is of interest to those of us in the field of sleep medicine, because it gives some insight into who is taking the examination, the reasons why, as well as some other useful information concerning basic practice patterns. Of the 624 respondents, fully 87% plan to take the exam in November, with 10% planning to take it in 2011. Pulmonologists made up the largest group (74%) of individuals at the course, followed by neurologists at 10%, pediatricians at 5%, psychiatrists at 1%, and other (likely otolaryngologists, internists, and family medicine practitioners) making up 10% of participants. These data are somewhat different than the demographics of the 2007 ARMS test takers, in which 69% were from the ABIM (being predominately pulmonologists), 23% were neurologists, 4% were pediatricians, and the remaining 6% were from various other fields. Given that the course was presented by the ACCP, the overwhelming predominance of pulmonologists attending the current course was not a surprise.

Most of the attendees preparing for the upcoming board exam are non-ABSM-boarded clinicians without formal fellowship training in sleep medicine. The majority (72%) of the respondents are in private practice, with the remaining 24% being in a clinical practice setting with some teaching responsibilities. Only 24% of the respondents have the old (ABSM) Sleep Board Credential and, as noted previously, the minority (18%) have completed a formal sleep medicine fellowship. Most (71%) spend 40% or less of their clinical time in the practice to sleep medicine, and 80% read 20 or fewer sleep studies a week. Despite recent changes in the acceptance of, and reimbursement for, portable sleep apnea testing by CMS, the overwhelming majority (81%) of the respondents never order or interpret portable sleep apnea studies.

For those of us in clinical practice, this overwhelming lack of adoption of portable sleep apnea testing is not a surprise for many reasons, including the lack of identification of the ideal monitoring device, as well as difficulty with reimbursement by CMS and commercial payers.

Finally, with regard to accreditation by the AASM, 60% of the respondents work primarily in an accredited laboratory, and 21% are accredited by the Joint Commission or other accrediting body. For those who currently are associated with labs that are not accredited by the AASM, 47% plan to go for AASM accreditation in the next 12 months. This push for AASM accreditation may largely be driven by the changes in reimbursement proposed by CMS that are set to take effect in 2010.

Overall, the course was an overwhelming success. While the final evaluations from all of the course attendees are not yet available, the overwhelming majority (75%) of almost 600 of the participants who have completed their evaluations rated the course as excellent overall. One attendee described the course as “the best organized and most comprehensive course that I have ever taken. A home run.” Similar comments have been echoed by many other attendees. The astounding attendee turnout and overall outstanding evaluations are a testament to the group of professionals, including lecturers and ACCP support staff, who made presenting this course a pleasure and an honor. Good luck to everyone on the upcoming board exam in November!

This Month in CHEST: Editor’s Picks

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


► 18F-FDG-PET/CT Imaging of Lungs in Patients With Cystic Fibrosis. By Dr. M. Kain, et al.

► “Real-World” Effectiveness of Reactive Telephone Counseling for Smoking Cessation: A Randomized Controlled Trial. By Dr. A. Sool, et al.

TRANSPARENCY IN HEALTHCARE


SPECIAL FEATURE

► Does Statin Use Improve Pneumonia Outcomes? By Dr. V. Chopra; and Dr. S. A. Flanders.

TRANSLATING BASIC RESEARCH INTO CLINICAL PRACTICE

► New Mechanisms of Pulmonary Fibrosis. By Dr. R. M. Strieter; and Dr. B. Mehraad.

www.chestjournal.org

PCCU Lessons for November

► Emerging Occupational and Environmental Respiratory Diseases. By Dr. Paul D. Blanc, FCCP

► Therapeutic Hypothermia. By Dr. Mark D. Siegel, FCCP; and Dr. Peter S. Marshall
Critical Care Societies Collaborative Takes On New Issues

HHS has asked the group to help reduce catheter-related bloodstream infections in ICUs.

The four major critical care professional and scientific societies have recently renamed their collaborative group as the Critical Care Societies Collaborative. The societies, previously often referred to as the “Quad Societies,” include the American Association of Critical-Care Nurses (AACN), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM). This group of societies has been working together on a number of topics for the past decade and, recently, has had an opportunity to collaborate on several important new areas.

For example, the US Department of Health and Human Services (HHS) has asked the Critical Care Societies Collaborative for its help in creating an education campaign aimed at the members of the four societies and others working in our nation’s ICUs to reduce catheter-related bloodstream infections. The campaign, if included in the department’s FY 2011 budget, would be part of a larger effort by HHS and other government and private organizations to reduce hospital-acquired infections.

After a meeting in August with Dr. Don Wright, the principal deputy assistant secretary for health and the HHS official responsible for hospital-acquired infections, the Collaborative agreed to work together to submit a proposal for an educational campaign. Program components discussed in the meeting include Web-based tools, an interactive database, and in-person educational sessions.

I know speak for the leaders of the other societies when I say how gratified we were that the HHS is looking to our professional organizations to achieve its goals,” said ATS President Dr. J. Randall Curtis, FCCP, who attended the August meeting, which was part of a retreat for the leaders of the collaborative associations.

“Our work with HHS on reducing hospital-acquired infections is just the first project in what we hope will be a series of future projects with HHS to address innovative ways to improve patient care,” stated Dr. Kalpalatha K. Gunupalli, FCCP, ACCP President. Last year, the Collaborative, along with the National Association for Medical Direction of Respiratory Care and the Society of Hospital Medicine, worked together to get the Office of Human Research Protections (OHRP) to reconsider a ruling that Michigan hospitals should have gotten patient consent when instituting an “ICU checklist” that had already been proven to reduce catheter infections. In the end, OHRP agreed with the Collaborative’s view, and HHS went on to support, and even highlight, the checklist as an effective tool for preventing these infections.

You can read more about the Collaborative’s letter regarding OHRP’s ruling about the Keystone project and also the Collaborative’s guidance for critical care clinicians interested in understanding the potential overlap between clinical research and quality improvement in the ICU at www.chestnet.org/practice/advocacy/positionPapers/08archives.php. The Collaborative is also considering ways to prevent ventilator-acquired pneumonia by examining the definition of the condition research priorities for VAP prevention, detection, and treatment; and the potential roles of various federal agencies in addressing these research issues.

During its July meeting, the Collaborative also agreed to send an Open Letter to President Barack Obama and congressional leaders (below) to support initiatives, including reimbursing physicians for talking with patients and their families about end-of-life issues, that the four societies believe would lead to more compassionate care for those who are dying.

Among other recommendations, the critical care associations encouraged the development of “incentives for clinicians, both in the inpatient and outpatient setting, to spend time talking with patients and their families and significant others about their values, treatment preferences, and goals of care at the end of life and document these discussions so they are available when needed.”

Open Letter to President Barack Obama and Congressional Leaders

From the Critical Care Societies Collaborative

The Critical Care Societies Collaborative represents four US-based critical care professional societies whose members include 100,000 clinicians and scientists. Critical care is a specialty that provides care for the sickest of sick—working in intensive care units (ICUs) with patients that require technological and expensive life-sustaining treatments.

Our Collaborative is extremely excited about the opportunities that exist for healthcare reform to dramatically improve the delivery of end-of-life care to patients with critical illness in the United States. We are distressed to hear discussion of removing improvements in end-of-life care from the agenda in response to misinformation that equates improvements in end-of-life care with rationing care or denying life-sustaining treatments to those who want it. Improving end-of-life care in acute and critical care represents a rare opportunity to improve quality of life and simultaneously reduce costs. Our nation cannot afford to let improving end-of-life care become a casualty of the healthcare reform debate.

Why should critical care societies care about end-of-life care? One in five deaths in the US occurs in the ICU. Studies suggest that when patients and families have earlier and more effective communication about end-of-life care, the result is higher quality end-of-life care that minimizes ineffective life-prolonging treatments and its associated costs and also improves quality of life and reduces symptoms. Consequently, improving the communication about end-of-life care offers us one of those rare opportunities to simultaneously improve quality of care and reduce costs.

We believe healthcare reform has the potential to dramatically improve the quality of end-of-life care in the US and simultaneously reduce costs of care with some simple and straightforward steps.

Promote thorough and careful completion of advance directives with the guidance of knowledgeable and skilled clinicians in outpatient and community settings and with appropriate review when patients’ condition or circumstances change.

Provide support for training clinicians in effective communication techniques.

Develop incentives for clinicians, in both inpatient and outpatient settings, to devote time talking with patients, families, and significant others about patients’ values, treatment preferences, and goals of care at the end of life and document these discussions so they are available when needed.

Develop incentives for hospitals and other components of the healthcare system to coordinate advance directives and improve communication about end-of-life care across institutions and settings. Does this involve withholding life-sustaining treatments from those who request this care? Absolutely not. We support, for anyone who wants it, using all measures that are indicated and can successfully sustain a person’s life. However, much of the rhetoric opposing incorporation of end-of-life care into healthcare reform legislation makes the false assumption that such efforts will result in withholding life-sustaining treatments from those who want such treatment.

On the contrary, we believe that healthcare reform can dramatically improve the quality of healthcare for patients with life-limiting illness or injury simply by ensuring that informed patients and families get the care that they would choose if they were fully informed. We also believe that facilitating communication around these difficult issues will likely be a source of great comfort for patients and their loved ones.

Unfortunately, our current system does not allow many patients and families to make informed choices in a timely way, doesn’t train clinicians to facilitate these difficult conversations with patients and their families, and doesn’t encourage clinicians to conduct these conversations.

Furthermore, our fragmented system means that even if a clinician does take the time to have such a conversation, the information learned from the patient about their values, goals, and treatment preferences is often not disseminated to other clinicians that care for that patient. We firmly believe that improving the quality of care we provide and reducing costs can be accomplished without withholding the desired level of care from anyone. But we need to change the way our healthcare system is organized and the way that clinicians and hospitals prioritize end-of-life care.

We will be missing an enormous opportunity if we allow misinformation to remove improvements in end-of-life care from healthcare reform legislation. We sincerely hope that our government has the wisdom and fortitude to combat misinformation and to retain efforts to improve end-of-life care in the legislation.

Dr. J. Randall Curtis, MD, MPH
President, American Thoracic Society

Beth Hammer, RN, MSN
President, American Association of Critical-Care Nurses

Kalpalatha K. Gunupalli, MD
President, American College of Chest Physicians

Mitchell M. Levy, MD
President, Society of Critical Care Medicine
NEWS FROM THE COLLEGE

EDUCATION INSIGHTS

Tobacco Dependence Treatment

BY SANDRA ZELMAN LEWIS, PhD
Assistant Vice President, Health and Science Policy

The American College of Chest Physicians (ACCP) demonstrated the new Tobacco Dependence Treatment Tool Kit at CHEST 2009. This tool kit is a comprehensive, evidence-based collection of background material and resources designed to assist physicians and other professionals in providing successful treatment for their tobacco-using patients. Now physicians can be reimbursed for discussing cessation treatment, so information on how to code for these services is provided also.

Tobacco dependence is a chronic medical condition, and physicians are encouraged to treat it as such, just as they would asthma, diabetes, or other chronic conditions. This means that patients should be placed onto a treatment protocol, managed, and followed to assess whether symptoms are improving or the protocol needs to be altered. Similar to the treatment of asthma, the recommended approach calls for the combined use of a long-acting controller-type medication and a short-acting reliever to alleviate breakthrough withdrawal symptoms. Other modalities, such as behavioral interventions, quit lines, and support groups, are also encouraged.

This is the 3rd edition, now online, of the previously titled Tobacco Cessation Tool Kit. New to this edition are treatment algorithms, updated pharmacotherapeutic guidance, many new tools, and a video demonstrating how to successfully adopt the therapeutic approach with tobacco-dependent patients. Many of the tools can be downloaded directly to your PDA. This edition also promotes creating teachable opportunities for pediatricians to work with tobacco-using parents to discuss the negative effects of second-hand smoke exposures. Information and resources for advocating on behalf of smoke-free legislation, information on tobacco treatment performance measures, and many additional resources are also contained in this new edition of the tool kit.

The ACCP Tobacco Dependence Treatment Tool Kit is now available online with unlimited access after a one-time purchase. However, during November 2009 to January 2010, all ACCP members will have that one-time payment waived, thus receiving free, unlimited access to all contents in this tool kit, now and in the future. Gain access at www.chestnet.org. Address questions to Sandra Zelman Lewis, PhD, slewis@chestnet.org, or Iram Azam at iazam@chestnet.org.

PRODUCT OF THE MONTH

CHEST 75th Commemorative Edition Available

Editors:
Dr. Loren J. Harris, FCCP
Dr. Glenn S. Tillotson, FCCP

This special publication highlights 75 seminal studies that have been published in CHEST since the first issue in March 1935. The top 12 are reprinted in this commemorative edition, and the citations for the remaining 63 articles are listed at the end. The edition also includes:

- "ACCP 1935-2009: An Inspiring History"
- "Introduction to 75 Years of Publishing CHEST"
- "Three Editors’ Perspectives," by Editors in Chief Dr. Alfred Soffer, Master FCCP, Dr. A. Jay Block, Master FCCP, and Dr. Richard S. Irwin, Master FCCP

Available from the ACCP Store at www.chestnet.org.

Important Safety Information

Adcirca should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure. If a patient experiences anginal chest pain after taking Adcirca they should seek immediate medical attention.

Adcirca contains the same ingredient (tadalafil) as Cialis, which is used to treat erectile dysfunction (ED). The safety and efficacy of combinations of Adcirca with Cialis or other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended.

Patients with a known serious hypersensitivity to Adcirca should not take Adcirca.

PDE-5 inhibitors, including Adcirca, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing Adcirca, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of Adcirca to these patients is not recommended.

The use of Adcirca with alpha blockers, blood pressure medications, and alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (fainting). Adcirca is metabolized predominantly by CYP3A in the liver. Use of Adcirca with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on Adcirca therapy that require treatment with ritonavir, Adcirca should be
ACCP Welcomes New CEO

Paul A. Markowski, CAE, is the new Executive Vice President and CEO for the American College of Chest Physicians. He succeeds Alvin Lever, FCCP(Hon), as only the fourth EVP and CEO in the society’s 75-year history.

Mr. Markowski comes to the ACCP with a robust background in health-care advocacy, communications, and organizational management. For the last 4 years, he has been the Deputy Executive Vice President and Chief Operating Officer at the American Academy of Otolaryngology – Head and Neck Surgery. Prior to that, he worked with the American Medical Association for 15 years, holding such positions as Director of Federation Relations and Advocacy Campaign Manager.

Mr. Markowski received a business degree from Marquette University, Milwaukee, WI, and has attained his CAE (Certified Association Executive). He holds memberships in the American Society of Association Executives (ASAE), the American Association of Medical Society Executives (AAMSE), and the Association Forum of Chicagoland. “I am truly honored to be only the fourth EVP and CEO of the ACCP. I am excited about the opportunity and look forward to working with a dynamic, forward-thinking organization,” noted Mr. Markowski.

His predecessor, Al Lever, held the CEO position at the ACCP for 18 years. “Under his stewardship, the ACCP has become recognized as the premier professional organization for practitioners of clinical chest medicine. We look forward to Mr. Lever’s continued consultation and support of the College and The CHEST Foundation,” commented Dr. James A. L. Mathers, Jr., FCCP, Immediate Past President of the College.

INTRODUCING A POWERFUL NEW THERAPY FOR PULMONARY ARTERIAL HYPERTENSION (PAH)

SIMPLE TO START
POWER TO MOVE

• Elimination half-life allows once-daily dosing
• No routine lab testing required
• Can be taken with or without food
• Available at retail and specialty pharmacies
• Reimbursement Hotline 1-877-948-9136

Adcirca, a phosphodiesterase type 5 (PDE-5) inhibitor, is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability

- Adcirca 40 mg at 16 weeks compared with placebo
  - 33-meter mean improvement of 6MWD in patients with PAH
  - 44-meter improvement in treatment-naive* patients
  - 23-meter improvement in background bosentan subgroup, p=NS
- 68% reduction in relative risk of clinical worsening with Adcirca 40 mg at 16 weeks compared with placebo†

Adcirca, a phosphodiesterase type 5 (PDE-5) inhibitor, is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability

discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with Adcirca, start Adcirca at 20 mg once a day. Use of Adcirca with potent inducers of CYP3A, such as rifampin, should be avoided. The use of Adcirca is not recommended for patients with severe renal or hepatic impairment. Please see full Prescribing Information for dosing recommendations for patients with mild to moderate renal or hepatic impairment.

In rare instances, men taking PDE-5 inhibitors (including Adcirca) for ED reported a sudden decrease or loss of vision or hearing, or an erection lasting more than four hours. A patient who experiences any of these symptoms should seek immediate medical attention.

The most common side effects with Adcirca seen in the PHIRST-1 clinical trial were headache, myalgia, nasopharyngitis, flushing, respiratory tract infection, extremity pain, nausea, back pain, dyspepsia and nasal congestion.

Please see brief summary of Prescribing Information on next page.

* Treatment-naive defined as no treatment with a prostacyclin or analogue, L-arginine, phosphodiesterase inhibitor within 4 weeks prior to study initiation.

† Not significant.


3. Data on file, United Therapeutics Corporation.
ADCIRCA® (tadalafil) Tablets

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please review the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability.

CONTRAINDICATIONS

Concurrent Organic Nitrates

Do not use ADCIRCA in patients who are using any forms of organic nitrite, either regularly or intermittently. ADCIRCA potentiates the hypotensive effects of organic nitrates. This potentiation is thought to result from the combined effects of nitric oxide and ADCIRCA on the nitric oxide/cGMP pathway.

Hypersensitivity Reactions

ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIRCA) or Glaus. Hypersensitivity reactions have been reported, including anaphylactic and anaphylactoid reactions.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin followed by intake of ADCIRCA. In at least 60% of deaths after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 24 hours of the nitrate, consider using a different antianginal agent. If nitroglycerin is required, the angina should be treated with nitrates. Patients with severe angina pectoris who are taking nitroglycerin should seek immediate medical attention.

Potent Inhibitors including gabapentin, have mild systemic vasodilator properties that may result in a transient decrease in blood pressure. Before prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be adversely affected by such effects. Patients with severe impaired arterial control of blood pressure or with left ventricular outflow obstruction (e.g., aortic stenosis and hypertrophic obstructive cardiomyopathy) may be particularly sensitive to the actions of vasodilators, including those containing tadalafil.

Use with Alpha Blockers and Antihypertensives

In patients requiring tadalafil, start at a dose of 20 mg once daily and increase to 40 mg once daily based upon individual tolerance. The use of potent inhibitors of CYP3A such as ketoconazole should be avoided because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Use in Patients with Mild to Moderate Hepatic Cirrhosis

Because of clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily.

Use with Potent CYP3A4 Inhibitors or Inducers

Currently available data on the effects of potent inhibitors of CYP3A4 on the pharmacokinetics of tadalafil are limited. Dose adjustments are not recommended in patients receiving potent inhibitors of CYP3A4 (e.g., ritonavir, saquinavir).

Use in Renal Impairment

In patients with severe renal impairment (creatinine clearance 10 to 30 mL/min), reduce the dose to 20 mg once daily. In patients with moderate renal impairment (creatinine clearance 30 to 60 mL/min), reduce the dose to 20 mg once daily b.i.d.

Use in Pregnancy

ADCIRCA is not recommended for use during pregnancy. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. There are, however, no adequately and well-controlled studies in pregnant women. Use of ADCIRCA in pregnant women should be avoided.

Use in Children

The safety and efficacy of ADCIRCA have not been established in children.

Pregnancy

ADCIRCA is a pregnancy category C drug. There are no adequate and well-controlled studies in pregnant women. Use of ADCIRCA in pregnant women should be avoided.

Nursing Mothers

It is not known whether tadalafil is excreted in human milk. Because many drugs are excreted in human milk, use of this drug in nursing women is not recommended.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

• Angina

Clinical Trials Experience

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. Clinical trials were conducted in 468 patients with PAH. ADCIRCA was compared with placebo in clinical trials. In trials for PAH, 251 and 251 patients were treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo group was 15% for ADCIRCA, 10% for placebo. The rates of discontinuation because of adverse events were similar for all treatment groups. ADCCIRCA was generally well tolerated in clinical trials. Table 1 presents treatment emergent adverse events reported by 2% or more of patients in the ADCIRCA 40 mg group and occurring more frequently than placebo.

Table: Treatment-Emergent Adverse Events Reported by 2% or More of Patients in ADCIRCA and More Frequent than Placebo by 2%

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Placebo (%)</th>
<th>ADCIRCA 20 mg (%)</th>
<th>ADCIRCA 40 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Back Pain</td>
<td>12</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 1: Treatment-Emergent Adverse Events Reported by 2% or More of Patients in ADCIRCA and More Frequent than Placebo by 2%

Potential Drug Interactions

The following interations have been identified during postapproval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, apparent frequency, lack of other alternative causation, or a combination of these factors. 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. Drug interactions may be more likely to occur when the combination of tadalafil and other agents are used in combination with drugs that are metabolized by the cytochrome P450 3A4 (CYP3A4) isoenzyme and have a narrow therapeutic index. Drug interactions may be more likely to occur if the potential for drug interactions is increased by factors such as age, renal or hepatic dysfunction, or concomitant use of multiple drugs. In some cases, the effects of drug interactions are not predictable, and the resulting reaction may be more severe than the reaction that would be predicted by the interaction of the individual components. This reaction may occur more frequently in patients with severe hepatic impairment (Child-Pugh Class C). The most common adverse events that have been associated with drug interactions involving tadalafil include: 1. Headache, 2. Chills, 3. Nausea and Vomiting, 4. Back Pain, 5. Muscle Spasm, 6. Constipation and 7. Angina.

Non-Medication Safety

In clinical trials, the most common adverse events were generally transient and mild to moderate in intensity. Table 1 presents treatment emergent adverse events reported by 2% or more of patients in the ADCIRCA 40 mg group and occurring more frequently than placebo.

Pulmonary Edema

In patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to low visual acuity ("counting fingers"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking, and is not possible to determine whether these events are related directly to the use of tadalafil, to the underlying systemic vascular risk or anatomic defect. It is not possible to predict the occurrence of such events, or other factors.

Non-Medication Safety

In clinical trials, the most common adverse events were generally transient and mild to moderate in intensity. Table 1 presents treatment emergent adverse events reported by 2% or more of patients in the ADCIRCA 40 mg group and occurring more frequently than placebo.

ADVERSE EFFECTS

Adverse reactions which have been observed in controlled clinical trials are listed below. These reactions are reported voluntarily from a population of treated patients and therefore, the frequency of the adverse events and its relationship to treatment is unknown. These reactions have been chosen for inclusion either because of their seriousness, apparent frequency, lack of other alternative causation, or a combination of these factors. 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. Drug interactions may be more likely to occur when the combination of tadalafil and other agents are used in combination with drugs that are metabolized by the cytochrome P450 3A4 (CYP3A4) isoenzyme and have a narrow therapeutic index. Drug interactions may be more likely to occur if the potential for drug interactions is increased by factors such as age, renal or hepatic dysfunction, or concomitant use of multiple drugs. In some cases, the effects of drug interactions are not predictable, and the resulting reaction may be more severe than the reaction that would be predicted by the interaction of the individual components. This reaction may occur more frequently in patients with severe hepatic impairment (Child-Pugh Class C). The most common adverse events that have been associated with drug interactions involving tadalafil include: 1. Headache, 2. Chills, 3. Nausea and Vomiting, 4. Back Pain, 5. Muscle Spasm, 6. Constipation and 7. Angina.
**Hypoglycemia Increased Mortality in CAP**

**BY KATE JOHNSON**

*Elsevier Global Medical News*

**MONTRÉAL** Patients with hypoglycemia at the time of hospitalization for community-acquired pneumonia (CAP) have an increased risk of death, compared with patients with normoglycemia, according to a study reported at the World Diabetes Congress.

“Hypoglycemia is an easy-to-measure variable on admission, and should be a red flag to alert physicians to possible high-risk pneumonia patients,” said John-Michael Gamble from the University of Alberta School of Public Health in Edmonton, Alta.

Because an influx of community-acquired pneumonia (CAP) cases resulting from pandemic influenza A (H1N1) is expected in hospital intensive care units, quick recognition of high-risk factors is particularly attractive, Mr. Gamble said.

His prospective study included 956 CAP patients admitted to six Edmonton hospitals between 2000 and 2002, for whom random venous blood glucose tests measured 6.1 mmol/L or lower. Hypoglycemia was defined as a measurement less than 4.0 mmol/L, and normoglycemia was defined as a measurement between 4.0 mmol/L and 6.1 mmol/L.

The primary outcome of the study was in-hospital mortality. Secondary outcomes included 30-day and 1-year mortality. The mean age of the patients was 65 years, and 15% resided in nursing homes.

Hypoglycemia was present at hospital admission in 54 patients (6%), among those patients, less than half (46%) were previously diagnosed diabetes patients. The mortality rate was significantly greater at all time points among patients with hypoglycemia at admission, compared with normoglycemic patients, reported Mr. Gamble. The in-hospital and 30-day mortality rates were both 20% for patients with hypoglycemia at admission, compared with 9% and 10%, respectively, in those with normoglycemia.

Similarly, at 1 year, patients with hypoglycemia at admission had a 35% mortality rate, compared with 23% in those patients with normoglycemia.

In addition to adjusting for age, sex, comorbidities, medication, and nursing home residence, the study adjusted for pneumonia severity index (PSI), smoking status, presence of advanced directives, previous pneumococcal vaccine, and direct admission to the ICU. Several additional sensitivity analyses included clinical markers of physiologic stress, exclusion of patients admitted to the ICU, and exclusion of patients with diabetes.

Whether high or low, blood glucose abnormalities in general “may serve as a marker for sicker patients,” commented Dr. Silvio Inzucchi, professor of medicine and clinical director of the section of endocrinology at Yale University, New Haven, Conn. Among nondiabetic patients, blood glucose abnormalities may be “particularly dangerous,” Dr. Inzucchi explained in a presentation at the meeting.

Endocrinologists and intensivists are facing a “pendulum swing” regarding in-patient glucose control, Dr. Inzucchi noted, in light of a recent publication suggesting “very surprisingly” that intensive versus conventional control of hyperglycemia is associated with a 15-fold increase in hypoglycemia and significantly higher mortality (27.5% versus 24.9%) (N. Engl. J. Med. 2009;360:1283-97). As a result, Dr. Inzucchi helped draft the recent American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control, which recognizes the potential hypoglycemic risks of intensive control and recommends relaxing target blood glucose levels (Diabetes Care 2009;32:1346-58). “In the case of CAP, we need to look at the risks and benefits of treating admission hypoglycemia,” commented Mr. Gamble.

Although Mr. Gamble’s study did not look at the causes of admission hypoglycemia, almost half of the study subjects had diabetes, with hypoglycemia likely resulting from their medication. “For the others, comorbidities that they had in addition to the pneumonia may have caused spontaneous hypoglycemia,” Mr. Gamble said.

Mr. Gamble said he had no conflicts of interest. Dr. Inzucchi declared paid lectures with Novo-Nordisk, an advisory board agreement with Medtronic, research sponsored by Eli Lilly Co., and CME program participation in which Sanofi-Aventis was a funding source.
Medical Imaging Can Add Up to High Radiation Doses

PERFOROMIST® (formoterol fumarate) Inhalation Solution
20 mcg/2 mL vial

BRIEF SUMMARY

The following is a brief summary; see full prescribing information for complete product information.

INDICATIONS AND USAGE

Maintenance Treatment of COPD
PERFOROMIST Inhalation Solution is indicated for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchial obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Important Limitations of Use

PERFOROMIST Inhalation Solution is not indicated to treat acute exacerbations of chronic obstructive pulmonary disease. (See WARNINGS AND PRECAUTIONS, Deterioration of Disease and Acute Epilepsy)

PERFOROMIST Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of PERFOROMIST Inhalation Solution in asthma have not been established.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Asthma-Related Deaths and Exacerbations
(See BOXED WARNING)

Data from a large placebo-controlled study in asthmatics showed that long-acting beta, agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta, agonists.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (1/1763.176 in patients treated with salmeterol vs 1/313.179 in patients treated with placebo). For this study of patients experiencing cardiac/or respiratory death may represent a class effect of the long-acting beta, agonists, including PERFOROMIST Inhalation Solution. It is study adequate to determine whether the rate of asthma-related death in patients treated with PERFOROMIST Inhalation Solution has been conducted.

Clinical studies with formoterol fumarate administered as a dry powder inhaler suggested a higher incidence of asthma exacerbations in patients who received formoterol than those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in asthma exacerbation rates between treatment groups.

Deterioration of Disease and Acute Epilepsy

PERFOROMIST Inhalation Solution should not be used for the relief of acute asthma, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. PERFOROMIST Inhalation Solution has not been studied in the relief of acute asthma and extra doses should not be used for that purpose. Acute asthma should be treated with an inhaled short-acting beta, agonist.

When the regular inhalation of PERFOROMIST Inhalation Solution patients who have been taking inhalated, short-acting beta, agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the use of these drugs and use formoterol for the symptomatic relief of acute respiratory symptoms. When prescribing PERFOROMIST Inhalation Solution, the healthcare provider should also prescribe an inhaled, short-acting beta, agonist and instruct the patient how it should be used. Increasing the inhaled beta, agonist use is a signal of deteriorating disease for which prompt medical attention is warranted. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If PERFOROMIST Inhalation Solution no longer controls the symptoms of bronchospasm, or if the patient’s inhaled, short-acting beta, agonist becomes less effective or the patient needs more inhalation of short-acting beta, agonist, than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken. Increasing the daily dosage of PERFOROMIST Inhalation Solution beyond the recommended 20 mcg twice daily dose is not appropriate in this situation.

Excessive use of PERFOROMIST Inhalation Solution and Use with Other Long-Acting Beta, Agonists

As with other inhaled beta, agonists, PERFOROMIST Inhalation Solution should not be used more often, or at higher doses than recommended, or in conjunction with other medications containing long-acting beta, agonists; an overt result may occur. Significant clinical cardiovascular effects and fatalities have been reported in association with excessive use of inhalated sympathomimetic drugs.

Paradoxical Bronchospasm

As with inhaled beta, agonists, PERFOROMIST Inhalation Solution can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, PERFOROMIST Inhalation Solution should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects

PERFOROMIST Inhalation Solution, like other beta, agonists, can produce a clinically significant cardiovascular response in some patients as measured by increased heart rate, systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, PERFOROMIST Inhalation Solution may need to be discontinued in addition, beta-agonists have been reported to produce ECG changes, including flattening of the T wave, prolongation of the QTC interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shifting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium may require a decrease in the potassium supplement. Beta-agonist medications may produce transient hyperglycemia in some patients.

Clinically significant changes in serum potassium and blood glucose were infrequent during clinical studies with long-term administration of PERFOROMIST Inhalation Solution at the recommended dosage.

ADVERSE REACTIONS

Long-acting beta, agonists such as formoterol may increase the risk of asthma-related death. (See BOXED WARNING)

Ble, Agonist Adverse Reaction Profile

Adverse reactions in PERFOROMIST Inhalation Solution are expected to be similar in nature to other beta, agonist. receptor agonists including; alphastimulation, hypertension or hypotension, betaadrenergic effects, nervousness, headache, tremor, dry mouth, muscle cramps, agitation, nausea, diarrhea, fatigue, malaise, insomnia, hypokalemia, hyperglycemia, and metabolic acidosis.

Clinical Trials Experience

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.

(Again with COPD)

The data cited below reflect exposure to PERFOROMIST Inhalation Solution 20 mcg twice daily by oral inhalation in 286 patients, including 230 exposed for 6 months and 155 exposed for at least 1 year. PERFOROMIST Inhalation Solution was studied in a 12-week, placebo-controlled trial (123 subjects treated with PERFOROMIST Inhalation Solution) and a 52-week, active-controlled trial (463 subjects treated with PERFOROMIST Inhalation Solution). Patients were mostly Caucasians (95%) and about 57% (66%) between 40-60 and 60+ years old and had COPD with a mean FEV, of 1.33 L.

Patients with significant congenital cardiac and other medical diseases were excluded from the trials. Table 1 shows adverse reactions from the 12-week, double-blind, placebo-controlled trial where the frequency was greater than 2% in patients treated with PERFOROMIST Inhalation Solution group and in patients treated with placebo.

Table 1 Adverse Reactions from the 12-week, double-blind, placebo-controlled trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PERFOROMIST Inhalation Solution 20 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>120</td>
<td>105</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (7.5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (2.5%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>URI</td>
<td>3 (2.5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Infections</td>
<td>3 (2.5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (2.5%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Patients treated with PERFOROMIST Inhalation Solution 20 mcg twice daily in the 52-week open-label trial did not experience an increase in specific clinically significant adverse events was 4.1% for PERFOROMIST Inhalation Solution and 4.4% for placebo. There were no frequently occurring specific cardiovascular events in the 52-week open-label trial (frequency greater than or equal to 1% and greater than placebo). The rate of COPD exacerbations was 4.1% for PERFOROMIST Inhalation Solution and 7.9% for placebo.

DIAGNOSTIC TESTS

Respiratory

If additional inhaled corticosteroids are to be administered by any route, they should be used with caution for the symptomatic effects of corticosteroids may potentiate. (See WARNINGS AND PRECAUTIONS, Excessive Use and Use with Other Long-Acting Beta, Agonists, Cardiovascular Effects, Concomitent Use of Other Cardiac Amines, Hypokalemia and Hyperglycemia).

Cystic Fibrosis

Concomitant use with cystic fibrosis, may potentiate any hypokalemic effect of oral adrenergic agents (see WARNINGS AND PRECAUTIONS, Hypokalemia and Hyperglycemia).

Non-potassium Sparing Diuretics

The ECG changes and hypokalemia that may be produced from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, and in patients who are unusually responsive to sympathomimetic amines. Clinical experience with the concurrent use of beta-agonists with non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, and in patients who are unusually responsive to sympathomimetic amines. Clinical experience with the concurrent use of beta-agonists with non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, and in patients who are unusually responsive to sympathomimetic amines. Clinical experience with the concurrent use of beta-agonists with non-potassium sparing diuretics.
pelvis, arm or leg, head and neck (including brain), multiple areas (including whole body) and unspecified.

To account for the possibility of procedure overlap, subjects were limited to one procedure per day that involved the same type of technique and the same anatomical area, selecting the highest dose.

Estimates of typical effective doses from published literature were used to approximate radiation exposure for each imaging procedure. The effective dose is an imexact measure of the overall detriment biologic effect from radiation exposure.

Patients were stratified by gender and age; 52% were women. The researchers identified effective doses for each procedure during the 5-year period overall and for each age-based and sex-based group and categorized them by dose: low (no more than 3 mSv/year), the background level of radiation from natural sources in the United States, moderate (3-20 mSv/year, the upper annual limit for occupational exposure for at-risk workers, averaged over 5 years), high (20-50 mSv/year, the upper annual limit for occupational exposure for at-risk workers in any given year), and very high (greater than 50 mSv/year).

A total of 3,442,111 medical imaging procedures associated with 655,613 pa-
tients were identified in the 3-year period. The average number of procedures per person per year was 1.2 and mean number was 0.7/person per year. The mean effective dose was 2.4 mSv/person per year with a median effective dose of 0.1 mSv/year.

The proportion of patients undergoing at least one procedure during the study period increased with age—from 59% in those aged 18-34 years to 86% in those aged 60-64 years. A total of 79% of women underwent at least one procedure during the study period, compared with 60% for men (N Engl J Med 2009;361:494-5).

Moderate doses occurred at an annual rate of 199 per 1,000 patients. High and very high doses occurred at annual rates of 19 and 2 per 1,000 patients, respectively. "Each of these rates rose with advancing age," noted Dr. Fazel.

"Generalization of our findings to the United States suggests that these procedures lead to cumulative effective doses that exceed 20 mSv per year in approxi-

The findings are concerning, particularly for patients who undergo several imaging tests in a short period of time, Dr. Michael S. Lauer wrote in an accompanying editorial (N Engl J Med 2009;361:494-5). "There may be situations, particularly for patients who are elderly, where we need to keep in mind that multiple imaging procedures carry a risk.

Dr. Philip Marx, MPH, FCPP, comments: We have adopted new imaging procedures to aid in the diagnosis of many illnesses, many of which are directed toward the early detection of malignancy. However, even with good intentions, there may be unintended consequences.

Notes: © Day, L.P. 2009. All rights reserved. Printed in USA for USA residents only. 05/09 03-848-21 (B4).

Beta-blockers: Beta-adrenergic receptor antagonists (beta-blockers) and fenoterol may inhibit the effect of each other when administered concurrently. Beta-blockers block the cardioacceleratory effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study. IAC exposure approximately 2000 times human exposure at the maximum recommended daily inhalation dose, but at doses of 5 mg/kg (IAC exposure approximately 50 times human exposure at the maximum recommended daily inhalation dose) in the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg (IAC exposure was approximately 50 times human exposure at the maximum recommended daily inhalation dose) and above. This finding was not observed in the drinking water study, nor was it seen in mice.

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg (IAC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose) and females at doses of 20 mg/kg (IAC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose in the dietary study). The incidence of hepatocellular neoplasms was increased in the dietary study at doses of 20 and 50 mg/kg in females (IAC exposure approximately 300 and 750 times human exposure at the maximum recommended daily inhalation dose, respectively) and 50 mg/kg in males, but not at doses of 5 mg/kg (IAC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg (IAC exposure was approximately 50 times human exposure at the maximum recommended daily inhalation dose) and above. In chronically treated monkeys in the clinical setting and in monkeys used in these studies, the endometrial hyperplasia have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutation tests in bacteria and mammalian cells, chromosomal analyses in mammalian cells, uninduced or spliced OVA synthesis repair tests in rat liver hepatocytes and human fibroblasts, transfection assay in human fibroblasts and in Chinese hamster cells.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 450 times the maximum recommended daily inhalation dose in humans on a mg/m2 basis). No effects were found in the offspring of animals treated with formoterol fumarate, although they should be administered with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility: The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study. IAC exposure approximately 2000 times human exposure at the maximum recommended daily inhalation dose, but at doses of 5 mg/kg (IAC exposure approximately 50 times human exposure at the maximum recommended daily inhalation dose) in the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg (IAC exposure was approximately 50 times human exposure at the maximum recommended daily inhalation dose) and above. This finding was not observed in the drinking water study, nor was it seen in mice.

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg (IAC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose) and females at doses of 20 mg/kg (IAC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose in the dietary study). The incidence of hepatocellular neoplasms was increased in the dietary study at doses of 20 and 50 mg/kg in females (IAC exposure approximately 300 and 750 times human exposure at the maximum recommended daily inhalation dose, respectively) and 50 mg/kg in males, but not at doses of 5 mg/kg (IAC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg (IAC exposure was approximately 50 times human exposure at the maximum recommended daily inhalation dose) and above. In chronically treated monkeys in the clinical setting and in monkeys used in these studies, the endometrial hyperplasia have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutation tests in bacteria and mammalian cells, chromosomal analyses in mammalian cells, uninduced or spliced OVA synthesis repair tests in rat liver hepatocytes and human fibroblasts, transfection assay in human fibroblasts and in Chinese hamster cells.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 450 times the maximum recommended daily inhalation dose in humans on a mg/m2 basis). No effects were found in the offspring of animals treated with formoterol fumarate, although they should be administered with caution.
Segmentectomy Debated
NSCLC • from page 1

significant differences in perioperative morbidity or mortality or late postoperative lung function between the two procedures (Ann. Thorac. Surg. 1999; 69:615-22).

Patients in the LCSG trial had tumors with a median size of nearly 3 cm, but in the intervening time since they enrolled, improvements in cancer detection with CT scanning have made it possible to detect tumors smaller than 2 cm.

Furthermore, nearly one-third of the patients who underwent sublobar resection in that trial received a wedge resection, even though it is considered to be a “lesser procedure” than segmentectomy. Dr. Broadus Z. Atkins of the division of thoracic surgery at the Durham (N.C.) Veterans Affairs Medical Center said in an interview.

Subsequent retrospective studies of patients who underwent sublobar resection with segmentectomy or wedge resection for peripheral stage I NSCLC of 2 cm or less in size found survival rates similar to those of patients who underwent lobectomy. Further support for a 2-cm cutoff for performing segmentectomy came from the International Association for the Study of Lung Cancer’s decision to subdivide stage T1 NSCLC into T1A (2 cm or less) and T1B (2-3 cm), based on survival differences seen in an analysis of thousands of patients with stage I NSCLC, Dr. Altorki said in an interview.

A switch from lobectomy to lung-sparing surgical techniques such as segmentectomy or wedge resection for tumors less than 2 cm in size on CT is analogous to the evolution of the use of lumpectomy vs. mastectomy for small breast cancers detected by mammography, he said.

As diagnostic modalities and technologies improve, you find tumors at earlier and earlier stages. Therefore, the treatment options have to keep up with these improvements in technology. You cannot continue to offer the same treatments that were predicated on larger tumors that are more advanced,” said Dr. Altorki, professor of cardiothoracic surgery and director of the division of thoracic surgery at New York-Presbyterian Hospital, New York.

To determine if disease-free survival after sublobar resection (segmentectomy or wedge resection) is noninferior to lobectomy, Dr. Altorki and his colleagues are currently enrolling patients at about 120 centers in the United States, Canada, and Australia in a phase III trial (labeled as Cancer and Leukemia Group B 140503). They hope to randomize more than 700 patients with pathologically confirmed, stage IA NSCLC 2 cm or less in size and negative lymph nodes in the hilum and mediastinum to either procedure. They plan to use either open surgery or video-assisted thoracoscopic. Patients will have follow-up visits every 3 months for the first year, then every 6 months in the second year, and annually for up to 5 years. Final outcomes for the trial’s primary end point will not be available until 2012.

If the CALGB 140503 trial demonstrates equivalent survival between the two procedures, segmentectomy should preserve lung function in patients who intrinsically have less lung function because of their age and status as current or former smokers. Patients who develop a second primary tumor after being cured of the first one will have more treatment options for the second tumor, he said.

Dr. Altorki noted that a similar, but randomized trial is underway in Japan.

Dr. Atkins said that he and his colleagues at the VA have been performing segmentectomy most often in patients who have undergone a previous lung resection or in those known to have poor lung function without a previous resection. The CALGB 140503 trial should help to determine if segmentectomy can be extended to patients who are otherwise “healthy” who would have previously undergone lobectomy, he said.

The trial is sponsored by the Cancer and Leukemia Group B, the National Cancer Institute, the Radiation Therapy Oncology Group, the American College of Surgeons Oncology Group, and the Southwest Oncology Group. For more information about the CALGB 140503 trial, visit clinicaltrials.gov/ct2/show/NCT00499330.

Dr. Richard Fischel, FCCP: comments:
This article accurately and succinctly describes a trial that is critical to the future treatment of lung cancer. We often quote the old data as a reason to reject a quart of lung tissue to remove a pea-sized tumor. The morbidity for older and sicker patients should not be underestimated.
Concurrent Therapy for Stage III NSCLC Spurs Debate

BY BETSY BATES
Elsevier Global Medical News

SAN FRANCISCO — Sacred cows may become an endangered species if Dr. Fergus Macbeth has his way.

A self-described heretic, the director of the Centre for Clinical Practice of the U.K. National Institute for Health and Clinical Excellence harbors serious doubts about the use of concurrent chemotherapy and radiation for patients with inoperable stage III non–small cell lung cancer.

Asked to speak on the topic, “When is Concurrent CT-RT Not the Treatment of Choice in Inoperable Stage III Disease?” at the World Conference on Lung Cancer, he had a simple answer: “Always.”

Punctuating his talk with slides of burnings at the stake, Dr. Macbeth argued that the trials pointing to level 1 evidence of superiority of concurrent CT/RT are not reflective of patients in the real world, that the survival gains are minuscule, and that the toxicity costs are great. From a practical standpoint, he noted, many eligible patients fail to receive concurrent therapy because medical oncology and radiation oncology at Emory University in Atlanta, opened the medical oncology session by reviewing the history of treatment for stage III disease.

Prior to the mid-1980s, most patients received what he termed “no chemo, no surgery, only ‘beamo,’” following a metastatic work-up with CT and bone scans. He described a standard 6-week course of radiation therapy (often including elective nodal irradiation) with fluoroura-based simulation. The 3-year median survival was 9.6 months.

The CALGB (Cancer and Leukemia Group B) 8433 trials ushered in a new paradigm by demonstrating a 4.1-month improvement in median survival when patients underwent a sequential regimen that began with chemotherapy (cisplatin and vinblastine), followed by radiation. Subsequent trials extended the survival window even further (to 19-27 months) when chemotherapy and radiation were given concurrently. “This represents a tripling of survival in a near doubling of treatment-related deaths when aggressive concurrent radiation and chemotherapy regimens are used. A nearly sixfold increase in esophagitis is also nearl... a remarkable improvement,” Dr. Curran said.

Dr. Macbeth’s point is that the devil is in the details of such trials, which he contends really reflect improvement in patients who have a good performance status and baseline hemoglobin, a small tumor volume, few comorbidities or rheumatic symptoms, and minimal weight loss.

All speakers agreed that only about 25% of patients present with such a rosy clinical picture. “What about the other 75% of patients?” There are few successful trials for them,” Dr. Curran acknowledged. “It is very difficult to define standard of care for lower [performance status] patients.” Elderly patients represent yet another challenge, even when they have a good performance status, he said.

Dr. Macbeth cited meta-analyses that show “spookily similar results,” namely, a 4%-5% improvement in survival, but a common malignancy … a remarkable improvement,” Dr. Curran said.

There was a near doubling of treatment-related deaths with concurrent radiation and chemotherapy.

DR. MACBETH

status and baseline hemoglobin, a small tumor volume, few comorbidities or rheumatic symptoms, and minimal weight loss.

Both results are salutary.

Sponsored Courses

<table>
<thead>
<tr>
<th>Date</th>
<th>Course Description</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 28 - 31, 2010</td>
<td>Sleep Medicine 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>April 30 - May 2, 2010</td>
<td>Ultrasonography: Fundamentals in Critical Care</td>
<td>Austin, TX</td>
</tr>
<tr>
<td>August 27 - 30, 2010</td>
<td>ACCP Pediatric Pulmonary Medicine Board Review 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>August 27 - 30, 2010</td>
<td>ACCP Sleep Medicine Board Review 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>August 27 - 31, 2010</td>
<td>ACCP Critical Care Medicine Board Review 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>August 31, 2010</td>
<td>Lung Pathology 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>August 31, 2010</td>
<td>Mechanical Ventilation 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>August 31, 2010</td>
<td>ABIM Critical Care Medicine and Pulmonary Disease SEP Modules</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>September 1 - 5, 2010</td>
<td>ACCP Pulmonary Medicine Board Review 2010</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>October 30 - November 4, 2010</td>
<td>CHEST 2010 Radiotherapy</td>
<td>Vancouver, BC, Canada</td>
</tr>
<tr>
<td>February 2010</td>
<td>Critical Care Bundle</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>February 2010</td>
<td>Basic and Advanced Bronchoscopy Skills With a Focus on Endobronchial Ultrasound</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>March 2010</td>
<td>Difficult Airway Management</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>March 2010</td>
<td>METI ISTAN Course</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>April 2010</td>
<td>Difficult Airway Management</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>April 2010</td>
<td>METI Emergency Care Simulator (ECS) Course</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>May 2010</td>
<td>Critical Care Bundle</td>
<td>Orlando, FL</td>
</tr>
</tbody>
</table>

COPD: What Really Works? A Best Practices Workshop for Primary Care

Coming to 20 US cities

Learn more and register at www.chestnet.org/copdedu

Learn more about ACCP-sponsored and ACCP-endorsed educational courses.

www.chestnet.org/education/calendar.php

(800) 343-2227 or (617) 498-1400

AMERICAN COLLEGE OF CHEST PHYSICIANS

2010 Education Calendar
Pemetrexed Improved Lung Cancer Survival

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

Results of a pivotal phase III trial that led to approval of pemetrexed as the first maintenance therapy in locally advanced or metastatic nonsquamous non-small cell lung cancer have been published online by the Lancet. Pemetrexed (Alimta) maintenance improved median overall survival by 2.8 months and median progression-free survival by 1.7 months in the placebo-controlled, 663-patient trial, according to the paper by lead author Dr. Tudor Chiricuta of the Cancer Institute Ion Chiriacuta, Cluj-Napoca, Romania, and his coinvestigators in the 20-country study (Lancet 2009 Sept. 19 [doi:10.1016/S0140-6736(09)61598-1]).

An accompanying commentary raised questions about the poststudy treatment of patients who progressed, however, and called for caution in interpreting the results (Lancet 2009 Sept. 19 [doi:10.1016/S0140-6736(09)61598-1]).

Eli Lilly & Co. sponsored the trial, which was conducted at 83 centers. The principal investigator, Dr. Chandra P. Belani of Penn State Cancer Institute in Hershey, Pa., presented the results earlier this year at the American Society of Clinical Oncology’s annual meeting.

Starting in March 2005, investigators enrolled 745 adult patients with advanced stage IIIIB or IV non–small cell lung cancer (NSCLC) that had not progressed during four cycles of platinum-based chemotherapies. After exclusions of 82 patients, mostly for not meeting study criteria, 663 patients were randomized on a 2:1 basis (441 to pemetrexed and 222 to placebo). Pemetrexed was delivered intravenously at 500 mg/m² on day 1 of 21-day cycles until disease progression. Both study arms also received best supportive care. Intent-to-treat analyses were based on all 663 patients at a median follow-up from randomization of 11.2 months.

Median progression-free survival, the primary endpoint, lasted significantly longer in the pemetrexed arm than the placebo arm (4.3 months vs. 2.6 months, respectively; hazard ratio, 0.50; P = less than .0001) by investigator assessment. The improvement in median overall survival also favored pemetrexed significantly (13.4 months vs. 10.6 months, HR, 0.79; P = .12). Response and disease-control rates were reported to be better in the pemetrexed arm as well.

Although grade 3 or higher adverse events were more common with pemetrexed (16% vs. 4%), as were drug-related discontinuations (5% vs. 1%), the investigators found the drug to be well tolerated and not the cause of any treatment-related deaths. However, a “striking difference” in the treatments that patients in the two arms of the trial received after disease progression was a cause for concern, noted the authors of the accompanying editorial, Dr. Thomas E. Stinchcombe of the University of North Carolina at Chapel Hill and Dr. Howard L. West of the Swedish Cancer Institute in Seattle. Just over half of the pemetrexed group (227 patients, or 51%) received systemic therapy vs. about two-thirds of the placebo arm (149 patients, or 67%).

Until the timing of maintenance therapy can be dissociated from differences in access to effective second-line therapies, they suggested the following: “For patients who have a response or stable disease with first-line chemotherapy, who tolerated platinum-based therapy without limiting toxicity while maintaining a good performance status, and who desire to continue therapy, maintenance therapy is an appealing consideration. However, if patients have had substantial toxicity with first-line therapy or desire a treatment-free interval, close monitoring and starting timely second-line therapy at disease progression remains an appropriate alternative.”

Some trial investigators, including Dr. Ciucaeanu and Dr. Belani, disclosed relationships with Eli Lilly: four of the study authors were company employees with stock ownership. Dr. Stinchcombe and Dr. West disclosed serving on the speakers bureau of Lilly Oncology.

Dr. W. Michael Alberts, FCCP, comments:
Most lung cancer treatment guidelines have suggested that patients with responsive or stable metastatic disease should continue to undergo chemotherapy for 4-6 cycles, followed by observation. Based on this study, “maintenance” chemotherapy in patients with nonsquamous stage IV lung cancer who have responded or have stable disease after initial chemotherapy may become a more frequently employed option.
Sleep Disturbances Linked to Poor Perinatal Outcomes

BY SUSAN LONDON
Elsevier Global Medical News

Seattle — Sleep disturbances during pregnancy increase the risk of adverse perinatal outcomes, such as gestational diabetes and cesarean delivery, according to an overview of research presented at the annual meeting of the Associated Professional Sleep Societies.

“Sleep disturbances are common during pregnancy,” said Bilgay Izci Balserak, Ph.D., of the University of Glasgow (Scotland) Sleep Centre. “The majority of pregnant women experience some level of sleep disturbance, especially in the third trimester of pregnancy.”

A 2007 poll conducted by the National Sleep Foundation, Washington, found that 84% of pregnant women reported experiencing sleep problems at least a few nights per week, she noted. This compared with 67% of all women surveyed.

Altered sleep during pregnancy stems from a variety of hormonal, physiologic, and psychological factors, according to Dr. Balserak. Those factors can affect sleep directly, as in the case of progesterone causing sedation, or indirectly, as in the case of heartburn or nocturia causing awakenings.

The sleep disturbances seen during pregnancy include both nocturnal perturbations (poor sleep quality, insomnia, and frequent awakenings) and daytime symptoms (fatigue and daytime sleepiness), she noted. Pregnancy-related changes can also trigger frank sleep disorders or exacerbate preexisting ones.

Providers should encourage women to adopt healthy lifestyle behaviors that may improve sleep.

Dr. BALSERAK

The acute sleep loss or fragmented sleep that result from sleep disturbances “can cause adverse perinatal outcomes,” she said. Retrospective and prospective studies, for example, have shown that pregnant women with sleep-disordered breathing have a two- to fivefold increased risk of developing gestational diabetes after body mass index is taken into account (Am. J. Respir. Crit. Care Med. 2007;175:A996, and Sleep 2009;32:A320-1).

Other research has linked sleep disturbances to birth outcomes. For instance, compared with women with a total sleep time of at least 7 hours in late pregnancy, women with a total sleep time of less than 6 hours or 6-6.9 hours have sharply elevated odds of cesarean delivery (odds ratios, 4.5 and 3.7, respectively) (Am. J. Obstet. Gynecol. 2004;191:2041-6).

Women sleeping less than 6 hours also have longer labor, on average, than those sleeping at least 7 hours (29 vs. 18 hours).

Several studies have found correlations between unfavorable sleep parameters in late pregnancy and elevated levels of depressive symptoms, both at that time and in the early post partum period, Dr. Balserak noted.

In a study conducted among women in the third trimester of pregnancy that used the Center for Epidemiologic Studies Depression (CES-D) scale, relative to their nondepressed counterparts (CES-D score less than or equal to 15), depressed women (CES-D score of 16 or greater) had a greater frequency of sleep disturbances overall, as well as a longer latency to sleep onset (J. Perinat. Neonatal Nurs. 2007;21:123-9).

“Early recognition, management, and treatment of sleep disturbances are important to prevent adverse perinatal outcomes,” Dr. Balserak asserted. However, she added, there are currently no practiced parameters when it comes to screening for and managing sleep disturbances during pregnancy. “Regarding management, nonpharmacologic interventions should be considered as the first choice, including lifestyle modifications and cognitive-behavioral therapy strategies,” she said.

Providers should encourage women to adopt healthy lifestyle behaviors, such as daily exercise, that may improve sleep, Dr. Balserak said. And they should counsel women about measures to address specific symptoms disrupting sleep, such as modifying eating habits to reduce heartburn.

“If pharmacological treatment is necessary, it should be used with caution due to potential side effects on the fetus,” she concluded.

Dr. Balserak reported that she had no relevant conflicts of interest.

Dr. Paul Selceky, FCCP, comments: In addition to the author’s findings, snoring during pregnancy is associated with an increase in hypertension, pre-eclampsia, and fetal growth restriction, all presumably related to obstructive sleep apnea. Although the snoring may be unique to pregnancy with the enlarged uterus and nasal congestion, untreated OSA can have serious implications. In that regard, continuous positive airway pressure (CPAP) has been shown to reduce nocturnal hypertension in pre-eclampsia.
Surgical Treatment of OSA Reduced CRP Levels

BY SUSAN LONDON
Elsevier Global Medical News

SEATTLE — Surgery for obstructive sleep apnea may reduce patients’ C-reactive protein (CRP) levels even if the procedure does not cure their apnea, new study data show.

"Although it’s controversial, there is certainly evidence that C-reactive protein (CRP) elevation is related to obstructive sleep apnea, with or without obesity," Dr. Michael Friedman said at the annual meeting of the Associated Professional Sleep Societies. "Evidence of the relationship to sleep apnea without obesity is the fact that many studies show that good continuous positive airway pressure (CPAP) compliance decreases CRP levels."

The study investigators’ first objective was to determine whether surgical treatment of obstructive sleep apnea (OSA) reduces CRP levels, explained Dr. Friedman, who is an otolaryngologist at the Rush University Medical Center in Chicago. "More important, because many of our patients treated with surgery are not cured, we sought to determine whether patients who are not cured also benefit by having a decrease in CRP level."

The investigators retrospectively reviewed the charts of all adult patients who underwent surgery for OSA at the medical center between 2004 and 2008, had a moderately elevated preoperative CRP level (greater than 0.1 mg/dL but less than 1.0 mg/dL), and had pre- and postoperative polysomnography data. All of the patients had tried and failed CPAP. Dr. Friedman noted.

The change in apnea-hypopnea index (AHI) before and after surgery was used to classify patients’ OSA as cured (AHI reduced by greater than 50% and AHI score less than 20), substantially improved (AHI reduced by greater than 50% but AHI score greater than 20), improved (AHI reduced by 20%-50%), unchanged (AHI reduced by less than 20), and worsened (AHI increased).

Results were based on 75 patients. Mean age was 47 years, and 79% of the patients were men. The surgical procedure was a uvulopalatopharyngoplasty in 51% of patients, and minimally invasive single-stage multilevel surgery in 49% of patients, according to Dr. Friedman. All patients had three palatal pillar implants placed in the midline and, if their uvula measured greater than 1.5 cm, a partial uvulectomy. In addition, all patients had radiofrequency treatment of the tongue base.

A comparison of pre- and postoperative data in the population overall showed that surgery was associated with a significant decrease in the AHI (from 48 to 30) and a significant increase in the minimum oxygen saturation during sleep (from 81% to 85%). Body mass index was unchanged.

According to the polysomnography criteria, OSA was cured in 24% of patients, substantially improved in 15%, improved in 24%, unchanged in 26%, and worsened in 11%. The AHI was significantly reduced from the preoperative level in all of the groups except for the patients who had a worsening of their OSA, Dr. Friedman reported.

In addition, the CRP level fell significantly from the preoperative level in patients whose OSA met the criteria for cure (from 0.341 mg/dL to 0.122 mg/dL). CRP levels also declined in those patients whose OSA was substantially improved (from 0.520 mg/dL to 0.314 mg/dL) or improved (from 0.355 mg/dL to 0.151 mg/dL).

"In this study, surgery reduced CRP levels even in those patients where cure was not achieved," Dr. Friedman said.

"The fact that elevated CRP relates to an increased risk of cardiovascular disease is clear," he commented. Therefore, by reducing levels of that inflammatory marker, surgery for OSA may ultimately lower patients’ cardiovascular risk.

Dr. Friedman reported that he had no conflicts of interest in association with the study.

Weight Loss Improved Sleep Apnea in Type 2 Diabetes

BY DENISE NAPOLI
Elsevier Global Medical News

 Losing an average of 1.8 kg (4 lbs) in a complete remediation of obstructive sleep apnea for 13% of overweight diabetes patients in one study, offering some of the first empirical support of weight loss as a treatment for the condition. Moreover, a significant increase in symptoms in patients whose weight did not change over the study period suggests that obstructive sleep apnea (OSA) is a rapidly progressing syndrome that will worsen without treatment in middle-aged obese adults with type 2 diabetes.

The study looked at 264 patients with type 2 diabetes, a body mass index greater than 25 kg/m², and mild, moderate, or severe OSA. Their average age was 61 years, the average BMI was 37, and 9% were women.

In all, 125 of these patients were enrolled in an intensive lifestyle intervention group, which prescribed 1,200-1,800 kcal/day (depending on weight) and 175 min/wk of physical activity. The remaining subjects were placed in a study group for obesity research and education, although no differences were observed in men, in participants with less severe OSA, and in participants who lost the most weight.

One of the study authors, Dr. Mark H. Sanders, is a consultant and holds financial interest in Philips Respironics, which manufactures and distributes sleep-monitoring devices. He is also a former speaker and consultant for pharmaceutical and device makers. No other authors disclosed any relevant conflicts of interest.
CHEST 23.qxp 10/29/2009 10:39 AM Page 1

ZVO000828 © 2009 Pfizer Inc. All rights reserved.
ZYVOX™—proven efficacy in nosocomial pneumonia, due to known or suspected MRSA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*MRSA: Methicillin-resistant Staphylococcus aureus.


Please see brief summary of prescribing information on adjacent page.