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The 70-80 U.S. hospitals offering ECMO could be swamped because the H1N1 virus is so widespread, said Dr. Robert H. Bartlett.

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 gases, ventilator pressure, the extent of shock, and other factors.

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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 38 adult and pediatric intensive care units (JAMA 2009 Oct. 12 doi: 10.1001/jama.2009.1496]).

On the first day of ICU admission, 81% of the patients required mechanical ventilation, and 33% required inotropes or vasopressors, often with high levels of sedatives to help them adapt to the ventilator. The median ICU stay was 12 days, as was the median time on mechanical ventilation.

"If, as expected, prevalence of 2009 influenza A(H1N1)

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INSIDE

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 IA 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

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Lung Function Preserved With New Inhaled Insulin

BY MIRIAM E. TUCKER
Elsevier 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 (Afresa) 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 A_{1c} as well as safety with up to 2 years' follow-up, said Dr. Amin, medical director, pulmonary, at MannKind Corp., Paramus, 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 the 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 (FEV_1) 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 FEV_1 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, versus 0.385 mL/min per year, he reported.

Mean Hb A_{1c} 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 eXxperience with inhalers.*

IN THIS ISSUE

WHO: Treat Severe H1N1 Flu With Antivirals

BY JONATHAN GARDNER
Elsevier 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, international public health officials said.

That advice, given by the World Health Organization in an updated guideline on the treatment of flu viruses, applies to all patients, including pregnant women, children younger than 5 years, and neonates. At-risk patients—infants and children less than 5 years, people over the age of 65, nursing home residents, pregnant women, and those with chronic comorbid conditions or immunosuppression—should be treated with one of these agents if they have mild to moderate uncomplicated clinical presentations. Physicians need not prescribe antivirals for otherwise healthy 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. ■

CHEST PHYSICIAN

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

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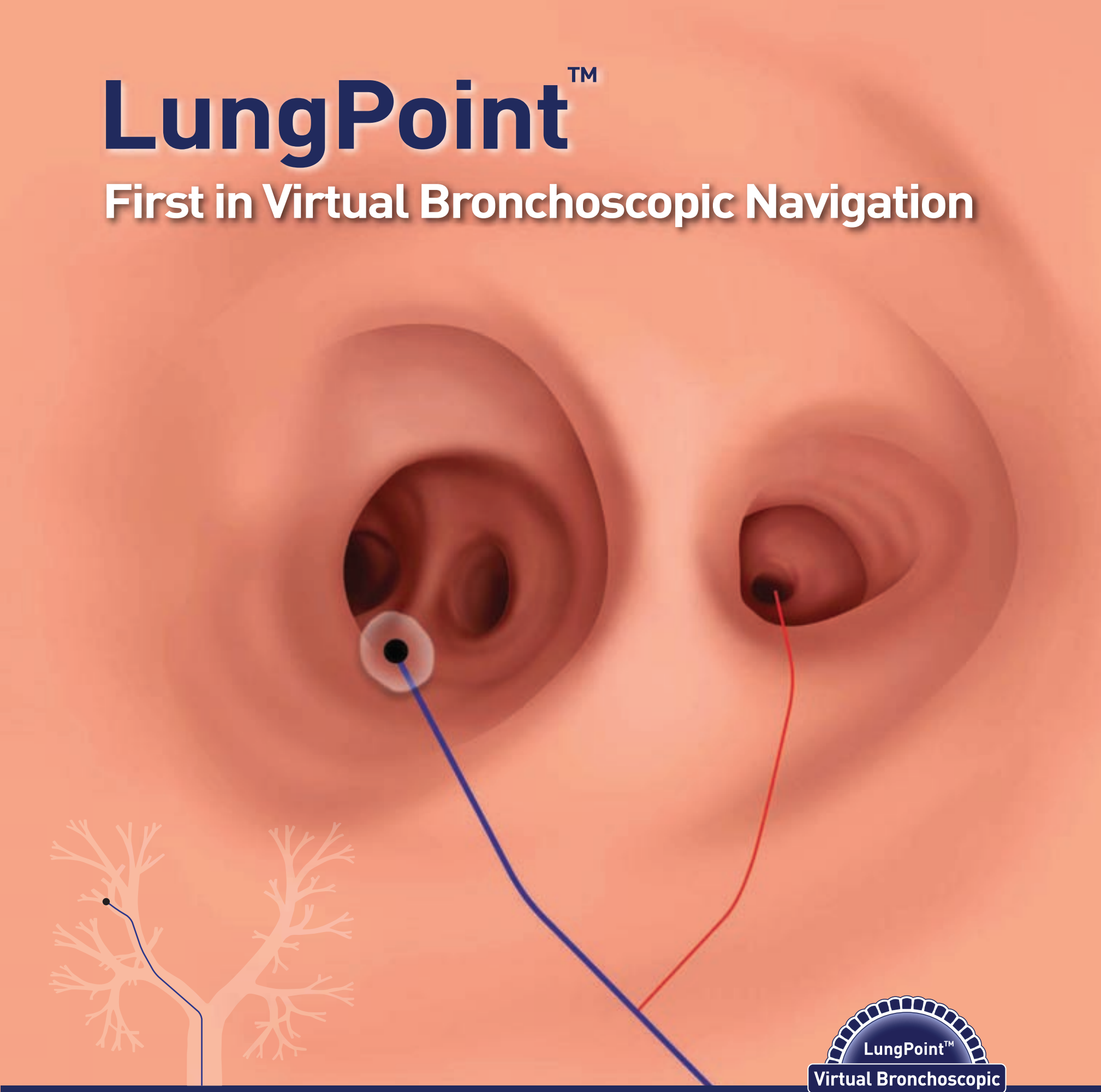

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Changes Coming to Lung Cancer Symptom Survey

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 (65%), 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 (with 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 differences, and not surprisingly, were pain—those with metastatic disease took the No. 6 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 titres following influenza vaccination, leaving this already at-risk population 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, Pharm.D., 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.

THE DECREASES IN ANTIBODY TITERS IN HEART FAILURE PATIENTS DROPPED BELOW THE THRESHOLD OF PROTECTIVE LEVELS, WHICH MADE THEM MORE SUSCEPTIBLE TO INFLUENZA.

Specifically, titer levels to the A(H3N2) viral strain fell from a peak of 320 to 60 post season in the healthy controls and from 160 to 30 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. The investigators determined that patients with heart failure had higher vaccine-induced interleukin-10 concentrations, suggesting a different cytotoxic T-lymphocyte phenotype for vaccine responses, and that heart failure patients mounted 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 reduced 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. Possible solutions that should be considered include higher doses of the vaccine, which might offer season-long seroprotection, or mid-season booster shots, she suggested.

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 code (**90470**) 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)

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 vaccination and counseling, 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 at 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 Drug Benefit After Study

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, the study, conducted 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 surveys 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 Hiangkiat Tan and colleagues suggested that the reason for the better outcomes among the oral medication users comes down to real-world usage patterns.

"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 poor 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 Pharmacy and Therapeutics Committee "chose to keep the oral controller used by the vast majority of its members on the same preferred formulary tier and lift its prior authorization requirement."

"Only 3% of patients in the ICS monotherapy 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, FCCP, 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 therapy 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
Elsevier Global Medical News

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 Esposito 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. As it turned out, 35 patients (47%) tested positive for RSV infection, and the remaining 39 (53%) did not.

Patients with RSV had significantly more cardiac arrhythmias and a significantly greater degree of abnormal heart rate variability than those without RSV. For example, approximately 25% of the patients with RSV had cardiac arrhythmias, compared with about 5% of those without RSV. Approximately 60% of the patients with RSV exhibited abnormal heart rate variability, compared with approximately 40% of those without RSV.

The investigators found no differences between the two groups in pulse oximetry, chest radiography, respiratory involvement, or cardiac troponin I levels.

The heart involvement appeared to be related to an RSV viral load of 100,000 copies per milliliter or more, and not to drug use or the disease's severity.

"This last finding suggests that RSV can be the direct cause of the heart damage and that arrhythmias can be found also in children with very mild RSV bronchiolitis in whom pulmonary hypertension and lung damage are nonexistent or marginal," the investigators wrote. "A careful heart evaluation has to be performed in all the children with RSV bronchiolitis."

The investigators reported that they had no conflicts of interest. ■

Study Will Test H1N1 Flu Vaccine in Pediatric Asthma

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

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 of 2009 H1N1 influenza vaccine that can be safely administered to this at-risk population and whether one or two doses are needed to provide an immune response that is predictive of protection," said Dr. Fauci, director of the National Institute of Allergy and Infectious Disease (NIAID).

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

DR. FAUCI

The study, sponsored by NIAID and the National Heart, Lung, and Blood Institute, plans to enroll 350-400 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. Participants assigned to the higher dose (30 mcg) will receive two injections of the 15-mcg vaccine at each administration.

In addition to studying adverse events, researchers will look for any effect the vaccine may have on asthma indicators. The study will last 34 weeks, according to a description at http://clinicaltrials.gov/ct2/results?term=H1N1+AND+asthma. It will be conducted in Georgia, Missouri, North Carolina, Ohio, Pennsylvania, Virginia, and Wisconsin. ■

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

BY DOUG BRUNK
Elsevier Global Medical News

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 mean body mass index (BMI) for the group was 17.5 kg/m^2, and one patient was considered to be obese.

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. However, only 13% of patients had a vitamin D blood concentration 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 D_3 for 1 year. After 1 year of treatment with vitamin D, 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

BY KERRI WACHTER
Elsevier Global Medical News

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."

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

With a similar incidence of ECMO use, the United States and the European Union could provide ECMO to approximately 800 and 1,300 patients, respectively, during their 2009-2010 winter season, the researchers wrote (JAMA 2009;302:doi:10.1001/JAMA.2009.1535).

The study by the Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators included all adult and pediatric patients who were treated with extracorporeal membrane oxygenation (ECMO) between June 1 and Aug. 31, 2009, in 15 ICUs in the two countries. Neonates and patients treated with ECMO for primary cardiac failure following heart and/or lung transplantation were excluded.

All outcomes were censored at midnight Sept. 7, 2009.

A total of 252 patients were admitted with influenza to the participating ICUs. Of these, 201 received mechanical ventilation. A total of 68 received ECMO; 61 had confirmed H1N1 infection. The 68 ECMO patients had a mean age of 34 years; half were male. The most common comorbidities were obesity (body mass index greater than 30 kg/m^2), asthma, and diabetes mellitus. Six patients were pregnant, and four patients were post partum. Three patients were children younger than 15 years.

Of the 68 ECMO patients, 48 survived to ICU discharge (32 were discharged from the hospital and 16 were still hospital inpatients). Fourteen patients (21%) had died, and six remained in the ICU.

Among the 14 patients who died, intracranial hemorrhage (6 patients), other hemorrhage (4), and intractable 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 54% 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. 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 than in the past, and data from a randomized, controlled trial showed a survival benefit using ECMO rather than conventional ventilation support for severe adult respiratory failure.

During a month-long "superepidemic" of H1N1 influenza in Australia earlier this year, 6% of hospitalized patients were admitted to the ICU, and 2% of all admissions (or 30% of ICU patients) were sick enough to be treated with ECMO, Dr. Bartlett said.

His institution recently had to cancel pediatric cardiac procedures because all of its ECMO systems were in use by six influenza patients. Since then, one ECMO system has been kept in reserve for conventional use in neonatology and cardiac surgery.

"A few years from now, when it's routine in any ICU, this will no longer be a problem. But right now, it's limited by the number of people who know how to run" current ECMO systems, Dr. Bartlett explained.

Dr. Charles Hoopes, FCCP, of the University of California, San Francisco, isn't convinced that ECMO will spread to every community hospital—or even that it should—but he does expect more demand for it.

"I think we're going to see a lot more ECMO," but its growth probably will mimic the development of artificial heart programs, in which smaller hospitals refer patients to tertiary-care centers with a higher volume of experience, he said.

That spoke-and-wheel model of care was tested in a study that randomized adults with severe respiratory failure to consideration for ECMO treatment or to conventional ventilation support and management. After 6 months, 57 patients (63%) in the ECMO group survived without disability, compared with 41 patients (47%) of 87 in the control group, reported Dr. Giles J. Peek of Glenfield Hospital, Leicester, England, and his associates in the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial (Lancet 2009 [doi:10.1016/S0140-6736(09)61069-2]).

Dr. Peek and several associates in the study are clinicians who provide ECMO services, and he and an associate received travel grants from Chalice Medical Ltd., which makes some of the equipment used in ECMO. The study was funded by public health systems in the United Kingdom.

Although the CESAR trial is the largest and best randomized study of adult ECMO referral, it is unlikely to end debate about ECMO's role in adult critical care, Dr. Joseph B. Zwischenberger, FCCP, and Dr. James E. Lynch argued in an editorial in the same issue (Lancet 2009 [doi:10.1016/S0140-6736(09)61630-5]).

Critics will point to the relatively modest 16% survival benefit, the risk of patients dying during transport to ECMO centers, some weaknesses in the current study's design, and previous data from more poorly designed studies that favored conventional management over ECMO, wrote Dr. Zwischenberger of the University of Kentucky, Lexington, and Dr. Lynch of the University of Texas, Galveston. The authors reported having no conflicts of interest related to the editorial.

"I think we're going to see an increase in respiratory failure secondary to viral necrotizing pneumonia, presumably related to H1N1 influenza" that will increase demand for ECMO, Dr. Hoopes said.

If the national level of ECMO beds can't handle demand, how should patients be triaged? What should the criteria be for referral to an ECMO center? And—perhaps the greatest quandary, he suggested—what should be done for young patients who don't recover on ECMO?

His institution and others—including Johns Hopkins University in Baltimore—have had to manage young adults with presumed H1N1 who did not recover respiratory function after weeks on ECMO. His program at UCSF has had some success in using ECMO as a bridge to lung transplant in these patients, 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]).

MANY HOSPITALS IN THE UNITED STATES MAY NOT HAVE ENOUGH PHYSICIANS WITH EXPERTISE IN THE NEEDED RESCUE THERAPIES.

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 should absolute scarcity occur," Dr. White and Dr. Angus wrote. "Any deaths from 2009 influenza A(H1N1) will be regrettable, but those that result from insufficient planning and inadequate preparation will be especially tragic."

Within the first 28 days of critical illness, 24 of the 168 patients died. An additional five patients died within 90 days, for an overall mortality rate of 17%. Of the deaths, 72% occurred in females.

The "striking" female susceptibility to influenza has not previously been described, according to the researchers. Studies during other pandemics have found that pregnancy is a risk factor for infection, and this may provide a partial explanation.

Of the 50 children admitted to the ICU, 4 (8%) died.

Virtually all of the ICU patients (98%) had one or more comorbidities, and 30% had a major comorbidity. Chronic lung disease was present in 41%, obesity in 33% (morbid obesity in 24%), and hypertension in 24%.

None of the investigators reported any relevant financial conflicts.

The Public Health Agency of Canada, the Ontario Ministry of Health and Long-Term Care, the Heart and Stroke Foundation Canada, and the Canadian Institutes of Health Research provided support for the Canadian study.

Dr. White received grant funding from the Greenwald Foundation and from the National Institute on Aging's Beeson Physician Faculty Scholars Program. ■

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. ■

SLEEP STRATEGIES

Who Is Taking the ABSM Sleep Medicine Board Exam?

BY DR. BARBARA PHILLIPS, FCCP
Sleep Institute Co-Chair
DR. NEIL FREEDMAN, FCCP
Sleep Institute Member
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 post-graduate 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 a rogue board, not recognized by the American Board of Medical Specialties (ABMS). Initially, the ABSM 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 conjointly 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 ABSM 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 prac ticing 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 have wanted 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 just offered. The 2009 sleep medicine board exam is the next-to-the last time one will be able to grandfather into sleep board eligibility. After 2011, candidates will have to have taken an American Council on Graduate Medical Education (ACGME)-accredited fellowship in order to be eligible.

We collected demographic data via an audience response system from individuals who 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 ABMS test takers, in which 65% were from the ABIM (being predominantly pulmonologists), 25% 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

▶ **Prospective Evaluation of Right Ventricular Function and Functional Status 6 Months after Acute Submassive Pulmonary Embolism: Frequency of Persistent or Subsequent Elevation in Estimated Pulmonary Artery Pressure.** *By Dr. J. A. Kline, et al.*

▶ **^{18}FDG- PET/CT Imaging of Lungs in Patients With Cystic Fibrosis.** *By Dr. M. Klein, et al.*

▶ **"Real-World" Effectiveness of Reactive Telephone Counseling for Smoking Cessation: A Randomized Controlled Trial.** *By Dr. A. Sood, et al.*

TRANSPARENCY IN HEALTHCARE

▶ **Sleep Deprivation, Physician Performance, and Patient Safety.** *By Dr. E. J. Olson, et al.*

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. Mehrad.*

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*

PCCU
PULMONARY AND CRITICAL CARE UPDATE

www.chestnet.org

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 following the meeting include Web-based tools, an interactive database, and in-person educational sessions.

"I know I 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. Guntupalli, 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.

'REDUCING HOSPITAL-ACQUIRED INFECTIONS IS JUST THE FIRST PROJECT IN WHAT WE HOPE WILL BE A SERIES OF FUTURE PROJECTS.'

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 often 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 care 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 take the time 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 are 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. ■

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

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

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

Mitchell M. Levy, MD
President, Society of Critical Care Medicine

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. ■

ACCP Welcomes New CEO

PAUL A. MARKOWSKI, CAE

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. ■

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 (WHO Group I) to improve exercise ability.

CONTRAINDICATIONS
Concomitant Organic Nitrates
Do not use ADCIRCA in patients who are using any form of organic nitrate, either regularly or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway.
Hypersensitivity Reactions
ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIRCA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS
Cardiovascular Effects
Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention.
PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.
Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIRCA is administered, the possibility of associated PVOD should be considered.
There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension

Use with Alpha Blockers and Antihypertensives
PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.
Use with Alcohol
Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.
Use with Potent CYP3A Inhibitors or Inducers
Co-administration of ADCIRCA in Patients on Ritonavir
In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Co-administration of Ritonavir in Patients on ADCIRCA
Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Other Potent Inhibitors of CYP3A
Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADCIRCA.
Potent Inducers of CYP3A
For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.
Use in Renal Impairment
In patients with mild or moderate renal impairment
Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.
In patients with severe renal impairment
Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.
Use in Hepatic Impairment
In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B)
Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily ADCIRCA.
In patients with severe hepatic cirrhosis (Child-Pugh Class C)
Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA.
Effects on the Eye
Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors.
Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.
Hearing Impairment
Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.
Combination with Other PDE5 Inhibitors
Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.
Prolonged Erection
There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.
ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).
Effects on Bleeding
PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
• Hypotension • Vision loss • Hearing loss • Priapism
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.
Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients.
In the placebo-controlled study, the most common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥ 9% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2%

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Headache	15	32	42
Myalgia	4	9	14
Nasopharyngitis	7	2	13
Flushing	2	6	13
Respiratory Tract Infection (Upper and Lower)	6	7	13

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2% (cont)

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Pain in Extremity	2	5	11
Nausea	6	10	11
Back Pain	6	12	10
Dyspepsia	2	13	10
Nasal Congestion (Including sinus congestion)	1	0	9

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.
Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.
Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis
Nervous — Migraine, seizure and seizure recurrence, and transient global amnesia
Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion
Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. 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 cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.
Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.
Urogenital — Priapism.

DRUG INTERACTIONS
Potential for Pharmacodynamic Interactions with ADCIRCA
Nitrates
Do not use ADCIRCA in patients who are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life–threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.
Alpha-Blockers
PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.
Antihypertensives
PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood–pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.
Alcohol
Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.
Potential for Other Drugs to Affect ADCIRCA
Ritonavir
Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.
Other Potent Inhibitors of CYP3A
Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA.
Potent Inducers of CYP3A
For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.
Potential for ADCIRCA to Affect Other Drugs
Cytochrome P450 Substrates
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).
Aspirin
Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.
P-glycoprotein *(e.g., digoxin)*
Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category B
Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.
Non–teratogenic effects
Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.
Nursing Mothers
It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.
Pediatric Use
Safety and effectiveness of ADCIRCA in pediatric patients have not been established.
Geriatric Use
Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.
Renal Impairment
For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.
In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.
Hepatic Impairment
Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

OVERDOSAGE
Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

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Hypoglycemia Increased Mortality in CAP

BY KATE JOHNSON
Elsevier Global Medical News

MONTREAL — Patients with hypoglycemia at the time of hospitalization for community-acquired pneumonia 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 25% 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 inpatient 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;32:1344-5). "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 lecturing 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

BY KERRI WACHTER
Elsevier Global Medical News

Medical imaging exposes a significant portion of patients to various doses of ionizing radiation, and in some cases, to substantial doses, potentially increasing the associated risk of cancer, according to findings of a retrospective cohort study.

The results are based on an analysis of 952,420 nonelderly adults who were enrolled in United Healthcare's database between Jan. 1, 2005, and Dec. 31, 2007, and living in one of five U.S. markets: Arizona, Dallas, Orlando, South Florida, and Wisconsin.

Roughly 70% of the study population underwent at least one imaging exam during the 3-year study period, "resulting in mean effective doses that almost doubled what would be expected from natural sources alone," wrote Dr. Reza Fazel, assistant professor of cardiology at Emory University, Atlanta, and her coinvestigators.

While most patients received less than 3 millisievert (mSv) per year—which was considered low exposure—there was a sizable minority of patients who received moderate, high, or very high radiation doses, they wrote.

CPT codes for imaging procedures involving radiation were used to identify claims from hospitals, outpatient facilities, and physicians' offices. They excluded procedures in which radiation was specifically delivered for therapeutic purposes, such as high-dose radiation for cancer. Procedures were categorized by technique: plain radiography, CT, fluoroscopy (including angiography), and nuclear imaging. They also categorized the procedures by area of focus: chest (including cardiac imaging), abdomen,

pelvis, arm or leg, head and neck (including brain), multiple areas (including whole-body scanning), 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 inexact measure of the overall detrimental biologic effect from radiation exposure.

Patients were stratified by gender and age; 52% were women. The researchers calculated effective doses for the population overall and for each age-based and sex-based group and categorized them by dose: low (no more than 3 mSv/year 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).

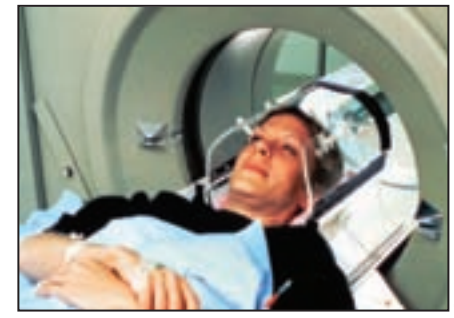
A total of 3,442,111 medical imaging procedures associated with 655,613 patients were identified in the 3-year period. The average number of procedures per person per year was 1.2 and median number was 0.7/person per year. The mean effective dose was 2.4 mSv/person per year with a median effective dose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

The proportion of patients undergoing at least one procedure during the study period increased with age—from 50% 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;361:849-57).

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 approximately 4 million Americans," the researchers wrote.

Myocardial perfusion imaging accounted for almost a quarter of the total effective dose (22%). CT of the abdomen, pelvis, and chest accounted for 38% of the total effective dose. "CT and nuclear imaging accounted for 21% of the total number of procedures and 71.4% of the total effective dose," the researchers reported. By anatomical site, chest procedures accounted for 45% of the total effective dose. Lastly, the bulk of the total effective dose—82%—was delivered in outpatient settings, primarily physicians' offices.



COURTESY NIH

Imaging may lead to cumulative annual doses above 20 mSv in 4 million people.

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;841-3). "Irradiation represents a direct danger imposed by a physician's decision to refer a patient for imaging. Though the danger may be small, it is cumulative and hence of particular relevance to the small but substantial minority of patients."

Physicians will need to take a careful history to assess the cumulative dose of radiation that a specific patient has already received, and this specific risk should be conveyed to the patient, noted Dr. Lauer, who is director of the prevention and population sciences division of the National Heart, Lung, and Blood Institute in Bethesda, Md.

Dr. Fazel reported that she has no relevant conflicts of interest, though several of her coauthors reported significant relationships with pharmaceutical and medical imaging companies. Dr. Lauer reported that he has no relevant conflicts of interest. ■

Dr. Philip Marcus, MPH, FCCP, 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 unintentional consequences. We need to keep in mind that multiple imaging procedures carry a risk.*

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. 1995; 60:615-22).

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.

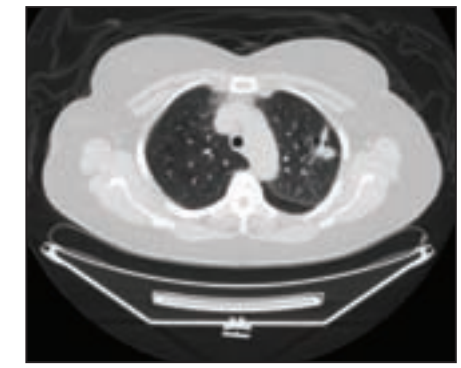
"As diagnostic modalities and technologies improve, you find tumors at earlier and earlier stages. Therefore, the treatment options have to keep up with these improvements in technology. You cannot continue to offer the same treatments that were predicated on larger tumors that are more advanced," said 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 thoracoscopy. 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 larger, 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.



Courtesy Dr. Mark F. Berry, Department of Surgery, Duke University Medical Center

CT shows peripheral NSCLC less than 2 cm and treated with segmentectomy.

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 resect 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 I 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 departments have difficulties coordinating the complex regimen.

The session generated heated questions from the audience, with many attendees insisting that the whole point of clinical trials is to determine in a controlled way which treatment approach is best. They scoffed at the notion of dismissing such hard-fought conclusions, particularly for patients who do fit the profile of those treated in clinical trials.

Dr. Walter J. Curran Jr., professor and chair of 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 fluoro-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 common malignancy … 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 thoracic symptoms, and minimal weight loss.

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

DR. MACBETH

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 near doubling of treatment-related deaths when aggressive concurrent radiation and chemotherapy regimens are used. A nearly sixfold increase in esophagitis is also troubling, he said at the meeting, which was sponsored by the International Association for the Study of Lung Cancer.

One possibility that has never been studied is the potential advantage of intensive continuous radiation therapy up front (as opposed to conventional regimens), followed by cisplatin-based chemotherapy, which might offer the same efficacy benefits of concurrent therapy without the problematic side effects, said Dr. Macbeth. "Give the most effective treatment first," he argued. "In my view, it's CHART [Continuous Hyperfractionated Accelerated Radiotherapy], and give it as soon as possible," he said.

Dr. Macbeth reported no financial disclosures. Dr. Curran has received consultant fees from AstraZeneca, Bristol-Myers Squibb Co., Genentech BioOncology, Eli Lilly & Co., and ImClone Systems Inc. ■

Dr. W. Michael Alberts, FCCP, comments: *Challenging conventional wisdom, even when that wisdom is based on solid experimental data, is often healthy. The challenge may confirm the conventional wisdom or may spur additional research. Both results are salutary.*

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 Ciuleanu of the Cancer Institute Ion Chiricuta, Cluj-Napoca, Romania, and his coinvestigators in the 20-country study (Lancet 2009 Sept. 19 [doi:10.1016/S0140-6736(09)61497-5]).

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 IIIB 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

Median progression-free survival lasted significantly longer in the pemetrexed arm.

DR. BELANI

(441 to pemetrexed and 222 to placebo).

Pemetrexed was delivered intravenously at 500 mg/m^2 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 end point, 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. Ciuleanu 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. ■

See an interview at www.youtube.com/watch?v=9S_-jhW_FoE.

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 practice 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 Selecky, 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 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 0.335 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 10.8 kg resulted in a complete remission 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/m^2, and mild, moderate, or severe OSA. Their average age was 61 years, the average BMI was 37, and 59% 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 enrolled in a less-intense "diabetes support and education" group, in which participants discussed diet, physical activity, and social support three times throughout the 1-year study (Arch. Intern. Med. 2009;169:1619-26).

As anticipated, the patients in the intensive lifestyle intervention group lost significantly more weight than did their counterparts in the low-intensity group (10.8 kg vs. 0.6 kg). But the lifestyle intervention group also saw a significant decrease in OSA symptoms (from 22.9 apnea or hypopnea events per hour to 18.3 per hour). The support and education group, meanwhile, saw an increase in events (from 23.5 to 28.3 per hour).

According to the study authors, led by Gary D. Foster, Ph.D., director of the center for obesity research and education at Temple University, Philadelphia, although future studies are needed to explore the reasons behind the OSA improvement, "more than [three times] as many participants in the [lifestyle intervention] group than in the [support and education] group had total remission of their OSA."

Researchers added that the prevalence of severe OSA among the weight-loss group was half that of their counterparts, and that the greatest benefits were observed in men, in participants with more severe OSA, and in participants who lost the most weight.

One of the study authors, Dr. Mark H. Sanders, is a scientific consultant to 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. ■

ZYVOX® linezolid injection, tablets and for oral suspension Brief summary of prescribing information.

INDICATIONS AND USAGE ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see **PRECAUTIONS, Pediatric Use**). **Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **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. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. **CONTRAINDICATIONS** ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal 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 types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). 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 re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone. **WARNINGS** **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 have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression.** In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality Imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections**. ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. 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 (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated. **PRECAUTIONS** **General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).** Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. 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 use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. *Phenylketonurics:* Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions** ***Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. *Adrenergic Agents:* Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. *Serotonergic Agents:* Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section. **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occured only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. **ADVERSE REACTIONS** **Adult Patients** The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators† (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events‡ were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators§ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events‡ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections‖ with ZYVOX (n=248) or cefadroxil (n= 251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocythemia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections‖ with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1 respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1# respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10^5/mm^3) 0.7 and 0.8; WBC (x 10^3/mm^3) 0.2 and 0.6; neutrophils (x 10^3/mm^3) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10^5/mm^3) 3.0 and 1.8; WBC (x 10^3/mm^3) 2.2 and 1.3 and neutrophils (x 10^3/mm^3) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections‖ were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10^5/mm^3) 0.0 and 0.4; WBC (x 10^3/mm^3) 0.8 and 0.8; neutrophils (x 10^3/mm^3) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10^5/mm^3) 12.9 and 13.4; WBC (x 10^5/mm^3) 12.4 and 10.3 and neutrophils (x 10^5/mm^3) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

* MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‡ The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

§ Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‖ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

¶ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

** <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

†† >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

‡‡ <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

^a^ >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

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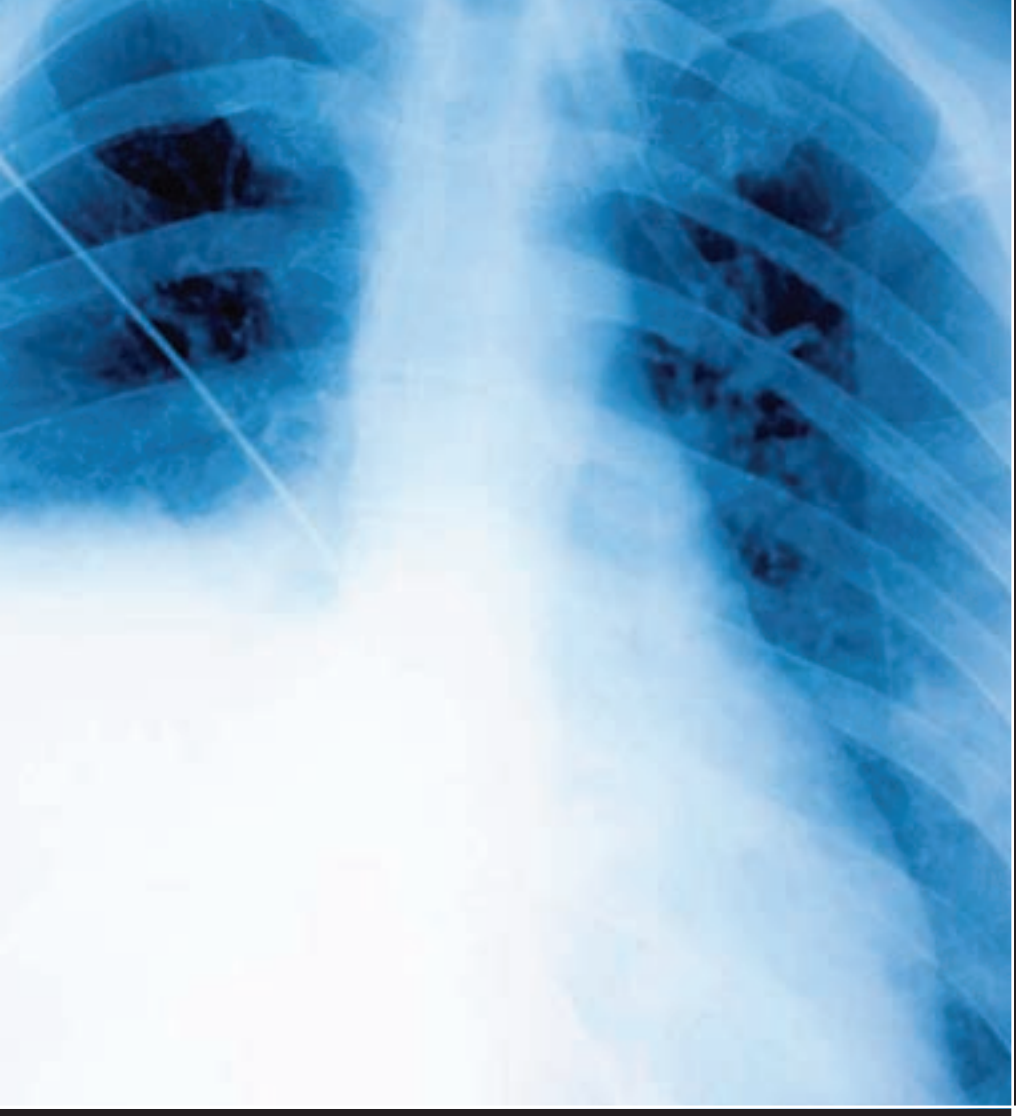

SERIOUS INFECTION

SERIOUS RESULTS

ZYVOX—proven efficacy in nosocomial pneumonia, due to known or suspected MRSA[1-3*]

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, vasopressive, and dopaminergic agents.

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

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

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

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

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

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

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

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

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

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

IV/Oral

ZYVOX®

(linezolid)

SMART BUG. SMART DRUG.™

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG, and the Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH, for the Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980-992. **3.** Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789-1797.

Please see brief summary of prescribing information on adjacent page.