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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



COURTESY ETHAN BICKFORD, CHILDREN'S HOSPITAL BOSTON

Susan J. Sommer and Dr. Elizabeth R. Woods lead the program, which reduced asthma-related ED visits and hospital admissions.

## Community Initiative Curbs Pediatric Asthma

BY SUSAN LONDON  
*Elsevier Global Medical News*

VANCOUVER, B.C. — An initiative that promotes improved asthma education and care at the family and community levels has reduced health care use and morbidity among disadvantaged children with asthma in Boston, according to Dr. Elizabeth R. Woods.

Four years into the Community Asthma Initiative, there was an 81% reduction in the percentage of participating children having asthma-related admissions, a 65% reduction in the percentage of children making emergency department visits, a 39% reduction in the percentage missing days of school because of asthma, and a 37% reduction in the percentage having limitations in physical activity because of the disease, Dr. Woods said at the annual meeting of the Pediatric Academic Societies.

The initiative targeted children from the four Boston neighborhoods with the highest asthma

rates and the greatest health disparities. The children and their families received case management and home visits by providers who helped them develop an individualized management plan, performed an environmental assessment, and supplied products such as vacuum cleaners with high-efficiency particulate air (HEPA) filters and bedding casings. Providers also instructed families in pest control techniques and connected them to community resources.

The initiative also targeted the community through an educational campaign and encouraged payers to address prohibitively high copayments for asthma medications.

Dr. Woods and her colleagues evaluated the effects of the initiative by analyzing parental reports and administrative data.

Results were based on 441 children (average age, 7.8 years) who had received case management through the initiative. Most were African American

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## Study Backs Low-Dose Oral Steroids For Acute COPD

*High-dose IV steroids weren't superior.*

BY MARY ANN MOON  
*Elsevier Global Medical News*

Low-dose oral corticosteroids are as effective as high-dose intravenous corticosteroids in the initial treatment of acute exacerbations of COPD, according to findings from a retrospective cohort study of nearly 80,000 COPD hospitalizations.

In the study, 92% of the patients were initially given high-dose IV corticosteroids instead of less-risky low-dose oral steroids. This contrasts sharply with recommendations favoring a low-dose regimen included in clinical guidelines published by leading professional societies in the United States, the United Kingdom, and other European nations, said Dr. Peter K. Lindenauer of the Center for Quality of Care Research at Baystate Medical Center, Springfield, Mass., and his associates.

Dr. Lindenauer and his colleagues compared outcomes with these two treatment approaches using a database designed to measure health care quality and utilization. They reviewed the records of 79,985 hospitalizations for acute exacerbation of COPD at 414 U.S. medical centers over a 2-year period.

The study participants had a median age of 69 years and had COPD that was uncomplicated by pneumonia or pulmonary embolism. The primary outcome was a composite measure of treatment failure, defined as the need for mechanical ventilation after the second day of hospitalization; death during hospitalization; or readmission for COPD within 30 days of discharge.

Overall, 11% of patients had this primary outcome, with approximately 1% requiring

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## Novel OSA Agents in Pipeline

BY BRUCE JANCIN  
*Elsevier Global Medical News*

SAN ANTONIO — Although obstructive sleep apnea is closely associated with obesity, not all the drugs being developed for the treatment of OSA are based on weight loss as their mechanism of benefit.

For example, acetazolamide addresses ventilatory instability,

which has emerged as a potential novel therapeutic target in OSA. Another early study suggests the sedative eszopiclone (Lunesta) reduces sleep apnea severity and increases sleep duration by raising the respiratory arousal threshold, investigators reported at the annual meeting of the Associated Professional Sleep Societies.

Still, weight loss is the classic

source of pharmacologic improvement in OSA. The first drug shown to be of benefit in OSA patients was sibutramine (Meridia), a serotonin and nor-adrenaline reuptake inhibitor, noted Dr. Ronald R. Grunstein, professor of sleep medicine at the University of Sydney.

He was lead investigator in a

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(Kantar Media Medical/Surgical Readership Study, June 2010)



# Pandemic Flu Reassortment Could Pose New Threat

BY DENISE NAPOLI  
Elsevier Global Medical News

Researchers are warning that the pandemic 2009 H1N1 influenza strain has been combining with other influenza strains among Hong Kong swine, and that further viral reassortment among global swine populations could again cause a pandemic in humans.

"The 2009 pandemic, although mild and apparently contained at present, could undergo further reassortment in swine and gain virulence," wrote Dr. Dhanasekaran Vijaykrishna and

associates at the State Key Laboratory of Emerging Infectious Diseases at the University of Hong Kong. The investigators called for greater surveillance in swine and recommended "that all eight gene segments are genetically characterized so that such reassortment events are rapidly identified."

In their study, Dr. Vijaykrishna and colleagues looked at tracheal and nasal swab samples taken from swine at a Hong Kong slaughterhouse between June 11, 2009, and Feb. 4, 2010. Samples were taken every 2 weeks on up to 252 swine per

sampling occurrence, for a total of 4,101 samples of unique swine. Overall, H1N1 and H1N2 viruses were isolated from 32 samples (Science 2010;328:1529).

Pandemic flu viruses "isolated on the same sampling occasion were genetically identical, suggesting transmission of viruses occurred within swine herds," the researchers said.

However, "viruses from different sampling dates were genetically distinct from each other and also from [2009 H1N1]-like swine viruses isolated in other countries, indicating multiple independent introductions of

these viruses from humans to swine," they said.

But the greatest concern comes from a January 2010 sampling where a novel reassortant was discovered; the new strain was named A/swine/Hong Kong/201/2010(H1N1). This novel strain—with a hemagglutinin gene most closely resembling European avian-based influenzas and a neuraminidase gene likely derived from the 2009 swine-derived H1N1 strain—could be particularly contagious.

"Neither [the 2009 H1N1] vaccine nor natural infection reliably elicits cross-protective

antibody to A/swine/Hong Kong/201/2010," they wrote.

Further laboratory testing of the new strain revealed that while the virus was susceptible to oseltamivir, it was resistant to adamantanes. Viral shedding occurred among the infected swine for up to 13 days.

"The introduction of [pandemic H1N1] virus to swine has provided it with opportunities for reassortment," Dr. Vijaykrishna and coworkers wrote. This "reservoir of reassortment" could, if left unchecked, "produce novel viruses of potential threat to public health." ■

## Weight Loss Not Only Target

OSA • from page 1

study that showed 6 months of sibutramine plus diet and exercise not only resulted in significant weight loss, but also brought marked improvement in OSA, reduced insulin resistance, raised

HDL cholesterol, and decreased visceral, subcutaneous, and hepatic fat, with no change in blood pressure (J. Clin. Sleep Med. 2009;5:416-21).

At the sleep disorders meeting, audiences learned of another weight-loss drug with evidence of efficacy for OSA: Qnexa, an investigational once-daily proprietary combination of phentermine and controlled-release topiramate.

Dr. David H. Winslow presented a double-blind, single-center trial in which 45 obese patients with OSA were randomized to once-daily Qnexa at 15-mg phentermine/92-mg topiramate CR or to placebo for 28 weeks. At week 8, the mean apnea-hypopnea index (AHI) in the Qnexa group had dropped from a baseline of 45.5 to 19.1 events per hour. By week 28, their mean AHI had fallen to 13.5, compared with 27.2 in the placebo arm, reported Dr. Winslow, a chest physician and president of the Kentucky Research Group, Lexington.

The Qnexa group experienced a mean 11% reduction in body weight over the 28 weeks, twice that of the placebo group. Other statistically significant changes in the Qnexa group included a mean 15-mm Hg drop in systolic blood pressure from a baseline of 138 mm Hg, compared with a 7.3-mm Hg drop in controls, along with improvements in arousal index and overnight oxygen saturation.

"I think we may be looking at a new paradigm in the treatment of OSA," Dr. Winslow said in an interview. Qnexa is under Food and Drug Administration review for a proposed indication as a treatment for obesity; a regulatory decision is expected later this year.

Danny J. Eckert, Ph.D., of Brigham and Women's Hospital, Boston, presented a double-blind, randomized, crossover trial in which 17 untreated OSA patients received 3 mg of eszopiclone or placebo immediately prior to going to sleep during overnight polysomnography on two occasions in the sleep lab.

The patients' mean AHI was 24 events per hour on eszopiclone, compared with 31 per hour with placebo. Patients on

eszopiclone also had a marked increase in total sleep time, from 5.3 hours on placebo to 6.8 hours, along with fewer arousals per hour and improved sleep quality, he reported.

Dr. Bradley A. Edwards, also of Brigham and Women's Hospital, presented a preliminary physiologic study in which six CPAP-treated patients with OSA underwent 2 nights of baseline polysomnography, and then took acetazolamide SR 500 mg twice daily for a week. This was followed by another 2 nights of polysomnography in which CPAP was intermittently turned down to subtherapeutic levels in order to see whether acetazolamide reduced ventilatory control instability. This indeed proved to be the case in all six patients. Moreover, five of the six patients experienced an associated reduction in AHI.

Dr. Winslow disclosed serving as a consultant to Vivus, which is developing Qnexa. Dr. Eckert's study was partly funded by a research grant from Separacor. Dr. Grunstein's study was supported by Abbott Laboratories. Dr. Edwards reported no financial conflicts. ■

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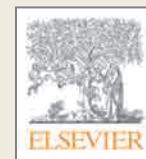
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# Iloprost May Prevent Lung Cancer in Former Smokers

BY CRAIG GUILLOT  
Elsevier Global Medical News

NEW ORLEANS — The oral prostacyclin analogue iloprost showed signs it could prevent some lung cancer in a study of 152 longtime current and former smokers.

Prostacyclin has proved to prevent lung cancer in mice. Authors of the current study, presented at an international conference of the American Thoracic Society, confirmed that oral doses of the drug can significantly improve dysplasia in former smokers.

The phase II clinical trial began with 71 former smokers and 81 current smokers, each with more than 20 pack-years of tobacco exposure. Subjects had to have at least mild sputum cytologic atypia and no previous history of cancer.

The researchers performed autofluorescence and white light bronchoscopy on each participant and biopsies of six standard endobronchial sites. These were scored 1-8 by World Health Organization criteria, where 1 is normal and 8 represents invasive cancer. Endobronchial histology was ranked in patients by three measures: worst biopsy score (Max), dysplasia index (DI), and the average of all biopsy scores (Avg).

Subjects were randomized to oral iloprost or a placebo in escalating doses for 6 months. A second fluorescent bronchoscopy was then performed along with a repeat biopsy of all the central airway areas sampled at the beginning of the study. The follow-up bronchoscopy was performed on 65 study participants in the placebo group and 60 in the iloprost group. Reasons for dropping out were ineligibility, toxicity, and refusal of further treatment.

Among former smokers, those in the oral iloprost group showed significant

COMMENTARY

**Dr. W. Michael Alberts, FCCP, comments:** Very few chemoprevention studies have shown benefit. This positive phase II study of oral iloprost in former smokers with dysplasia is encouraging. Let's hope that subsequent studies confirm the beneficial results.

improvement on all histologic measures, while former smokers receiving placebo showed declines. For the former smokers getting iloprost, the changes were 0.41 better in Avg, 1.1 points better in Max, and 11.6% better in DI than among those getting placebo. Current smokers did not show any such improvement in the drug or placebo groups.

The most common adverse effects exhibited in the original 75 members of the iloprost group included headache, flushing, and nausea.

The trial was led by Dr. Robert Keith of the Denver Veterans Affairs Medical Center and the University of Colorado, Denver. He has been testing several drugs to prevent lung cancer, and his disclosures included financial relationships with Pfizer and Boehringer-Ingelheim.

"This was the first study to show improvement, and I think this will ultimately go to a phase III trial and will involve people that are at the absolute highest risk" of lung cancer, Dr. Keith said. "I think we can now work closely with [the National Cancer Institute] to say that prevention is viable."

Iloprost is approved in inhaled forms to treat scleroderma, pulmonary hypertension, and Raynaud's phenomenon. The drug is marketed under the brand name Ventavis by Swiss drug maker Actelion and also comes in an intravenous form called Ilomedin. ■

# Sildenafil May Improve Quality of Life in IPF Patients

BY CRAIG GUILLOT  
Elsevier Global Medical News

NEW ORLEANS — Sildenafil might improve quality-of-life indicators in patients with idiopathic pulmonary fibrosis, according to the first multicenter, randomized trial to enroll patients at an advanced stage of the disease. However, the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) failed to show an effect of the drug on lung function, the study's primary end point.

The improvement in quality-of-life measures, a secondary end point in the study, is encouraging, said Dr. David A. Zisman, FCCP, of the interstitial lung disease program at the University of California, Los Angeles.

For the double-blind, placebo-controlled trial, the researchers recruited 180 participants from 14 IPF Clinical Research Network (IPFnet) centers across the country. Patients were randomized to receive oral sildenafil (20 mg, three times daily) or placebo for 12 weeks.

By the end of that period, nine subjects in the sildenafil group and six in the placebo group had increased their distance in the 6-minute walk trial by at least 20%—a standardized indicator of lung function. The difference was not significant.

But participants taking sildenafil had slightly better arterial oxygenation and reported less shortness of breath, Dr. Zisman said at an international conference of the American Thoracic Society. The study was also published online (N. Engl. J. Med. 2010 May 18 [doi:10.1056/NEJMoa1002110]).

The team did three tests of quality of life, including the St. George's Respiratory Questionnaire, in which a higher total indicates worse function. At 12 weeks, the sildenafil group had a total score of -1.64, and the placebo group scored 2.45.

On the Medical Outcomes Study

36-Item Short-Form Health Survey (SF-36), the sildenafil group better preserved its general health score, a subcategory of the test. The third quality-of-life test, the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), showed no significant difference.

"I think this mainly opens the door and promises another avenue to treat or slow progression of the disease," Dr. Zisman said. He added that sildenafil might be of value to patients with advanced IPF and that the data could prompt further trials. The results also suggest that phosphodiesterase type 5 inhibition might have a role in slowing disease progression, he said.

No major difference was seen in serious adverse effects with the drug and placebo. During the trial, two people died in the sildenafil group, and four died in the placebo group.

Sildenafil stabilizes cyclic guanosine monophosphate (cGMP) and leads to vasodilation in well-ventilated areas of the lung. It is manufactured by Pfizer under the brand names Revatio and Viagra.

Dr. Zisman disclosed that he is on the advisory board of Gilead Sciences. The STEP-IPF study was funded by the National Institutes of Health. ■

COMMENTARY

**Dr. Philip Marcus, MPH, FCCP, comments:** Sildenafil has been used for the treatment of pulmonary hypertension, and in the population of patients with IPF, many do develop pulmonary hypertension. Accordingly, whether sildenafil treats the disease or slows progression of IPF may be overshadowed by the ability of this PDE5 inhibitor to reduce pulmonary vascular resistance and improve quality of life.

# Low Dose as Effective

Steroids • from page 1

mechanical ventilation, 1% dying during hospitalization, and 9% being readmitted.

A total of 92% of patients were initially treated with high-dose IV steroids, and 8% were started on low-dose oral steroids. The composite outcome of treatment failure occurred in 10.9% of patients given high-dose IV steroids and 10.3% of those given low-dose oral steroids, a nonsignificant difference. Similarly, the individual outcome of in-hospital mortality was approximately 1% in both groups, they said (JAMA 2010;303:2359-67).

Further analysis showed that patients given oral steroids as recommended had lower hospital costs and shorter lengths of stay. Previous studies of the issue have shown that the oral route decreases patient pain and immobility, they added.

The findings clearly show that not complying with treatment recommendations and instead giving high-dose IV steroids to patients with acute exacerbations of COPD "does not appear to be associated with any measurable clinical benefit and at the same time exposes patients to the risks and inconvenience of an

intravenous line, potentially unnecessarily high doses of steroids, greater hospital costs, and longer lengths of stay," Dr. Lindenauer and his associates said.

"Because high-dose IV therapy is so common and because patients with COPD are hospitalized frequently for exacerbations, our findings have a significant potential to alter practice," they added.

Dr. Jerry A. Krishnan, FCCP, of the University of Chicago, and Dr. Richard A. Mularski, FCCP, of Kaiser Permanente and Oregon Health and Science University, Portland, commented in an editorial that the study shows that "real-world practice was largely inconsistent with current guideline recommendations to use lower

doses of corticosteroids administered orally."

Given the lack of clinical trial evidence regarding treatment options for exacerbations of acute COPD, they said, rigorous observational study data from studies such as this one "are sufficient to take action to change practice now" to support greater use of oral steroids. But "given that current practice overwhelmingly favors high-dose intravenous corticosteroids, facilitating change will be daunting."

The authors noted that the study was limited in that it was observational, the treatment assignments were not randomized, and the choice of therapy may have been influenced by symptom severity at presentation. ■

COMMENTARY

**Dr. Nicola A. Hanania, FCCP, comments:** The use of systemic corticosteroids in the management of acute exacerbations of COPD is essential and has been shown to affect clinical outcomes and rates of relapse of exacerbations. It is not known, however, whether intravenous high-dose

corticosteroids are superior to lower-dose oral corticosteroids in such circumstances. This report is based on an observational, retrospective analysis of a large database suggesting that both methods of administration are associated with similar outcomes. Similar observations have

been described in the management of acute asthma, as well. However, because the design of such a study may be associated with selection and treatment allocation bias, one cannot draw firm conclusions. Prospective studies to confirm these findings are needed.

temp: 101.9F

O<sub>2</sub> sat: 89%

WBC: 18.1

**MRSA**

**nosocomial pneumonia**

PMNs: 80% , bands: 15%

creatinine: 2.6

CXR: LLL infiltrate

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ZYVOX use is contraindicated in patients with 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 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-HT<sub>1</sub> 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.

\*Methicillin-resistant *Staphylococcus aureus*.

**References:** 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG; and 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(3):402-412. 2. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH; for 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(3):980-992. 3. Boselli E, Breilh D, Rimmelé T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med.* 2005;33(7):1529-1533.

Please see brief summary on adjacent pages.

# Cost of Care Cut in Half

Asthma • from page 1

(48%) or Latino/Hispanic (45%), and had public health insurance (70%).

Between baseline and 12 months, the proportion of children making asthma-related emergency department visits fell from 63% to 22%, hospital admissions due to asthma fell from 51% to 10%, and the proportion of children who missed days of school because of asthma dropped from 93% to 56%. In addition, the proportion of children who had

physical activity limitations due to asthma dropped from 55% to 35%.

The proportion of children with an up-to-date asthma action plan increased by 71% (from 49% to 84%).

In logistic regression analyses controlling for potential confounders, the children had significant 90%-100% reductions in the odds of each adverse outcome, noted Dr. Woods, a pediatrician at Children's Hospital Boston.

In the first year of the initiative, the cost of care per child was similar to that in a control neighborhood (\$1,335 vs. \$1,340). In the second year, it was approximately half as expensive in the initiative group (\$750 vs. \$1,322).

Dr. Woods noted that the initiative seems to be helping families in two main ways: understanding medications and addressing environmental issues. "Very few of these families had even a vacuum cleaner, let alone ones with HEPA bags and filters. These are incredibly helpful and much less costly than additional medication," she said.

COMMENTARY

**Dr. Burt Lesnick, FCCP, comments:** Education, use of asthma management plans, and improving the home environment can have an impressive positive effect on children's asthma morbidity and treatment costs. It would be interesting to see if subgroups could be identified, by phenotype or genotype, for which this comprehensive intervention is most effective.

**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<sup>1</sup>]). **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<sup>1</sup>]), 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), vasopressor 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-HT<sub>1</sub> 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 postimplantation 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 sternbrae, 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 occurred 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 (V<sub>ss</sub>) 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

# Selenium Failed to Prevent Second Lung Cancers

BY JANE SALODOF MACNEIL  
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CHICAGO — Selenium supplementation does not prevent second cancers in survivors of early-stage lung cancer—and may even make these patients more vulnerable to new tumors.

Indeed, although the differences did not reach statistical significance, patients who used supplements developed more second cancers, including lung tumors,

than those who did not take selenium in a randomized, controlled phase III chemoprevention trial that was stopped early for futility.

“We can say for sure that the selenium was not beneficial,” Dr. Daniel Karp said at the annual meeting of the American Society of Clinical Oncology, where he presented data on 1,522 patients who had been randomized from October 2000 to November 2009 and followed for a median of more than 4 years.

As of August 2009, the trial population had developed 216 second primary tumors, including 84 new lung cancers in 83 patients (one patient had two new lung tumors). The incidence of second primary tumors was 1.91 per 100 person-years followed in the selenium group vs. 1.36 per 100 person-years in the placebo group. Overall, the incidence of second primary tumors of any type after 1 year was 4.11% in the selenium cohort and 3.66% among those not given supplementation.

The progression-free survival rate at 5 years was also slightly better in the placebo group (78% vs. 72%), as was overall survival at 3 years (90% vs. 85%) and 5 years (80% and 75%).

The Eastern Cooperative Oncology Group (ECOG) started the intergroup trial after a study that failed to show selenium could prevent skin cancers suggested that it could reduce the incidence of lung, colorectal, and prostate cancers by as much as 30% (JAMA 1996;276:1957-63). The ECOG trial enrolled patients 6-36 months after complete resection of stage 1 non-small cell lung cancer. All had no sign of disease on biopsy.

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; thrombocytopenia 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 4.0; 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<sup>3</sup>/mm<sup>3</sup>) 0.7 and 0.8; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 0.2 and 0.6; neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 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<sup>3</sup>/mm<sup>3</sup>) 3.0 and 1.8; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 2.2 and 1.3 and neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 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) 2.4 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 9.5; 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<sup>3</sup>/mm<sup>3</sup>) 0.0 and 0.4; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 0.8 and 0.8; neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 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<sup>3</sup>/mm<sup>3</sup>) 12.9 and 13.4; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 12.4 and 10.3 and neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry†† 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†† 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-mane 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 <50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

§ >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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“We can say for sure that the selenium was not beneficial.”

DR. KARP

Randomization was 3:1 to 200 mcg daily of selenium yeast for 4 years or placebo yeast. Most patients had normal selenium levels when they entered the trial, said Dr. Karp, a professor of thoracic/head and neck medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston.

Particularly concerning, he noted, was that the amount of selenium in the supplement used in the trial is comparable to the amount in most daily multivitamins. “We need to find people who are deficient and make sure they have a normal amount,” he said, questioning the wisdom of giving supplements to everyone.

Also noteworthy was that active smokers had a 30% chance of developing lung cancer at 5 years vs. 24% for former smokers and 20% for never smokers. A subgroup of 94 never smokers had a slight trend toward benefit from selenium, he said.

One possibility Dr. Karp suggested in a press briefing is that antioxidants might have a harmful effect in the presence of carcinogens such as tobacco. Another study found worse outcomes—higher incidence of lung cancer and risk of death from the disease—in people who took beta-carotene (N. Engl. J. Med. 1996;334:1150-5).

Dr. Karp disclosed receiving research funding from Pfizer.

**Dr. W. Michael Alberts, FCCP, comments:** This study points out the potential danger of supplements. Not only did supplemental selenium fail to prevent second lung cancer, but those in the active medication group actually developed more second cancers. The latter did not reach statistical significance, but the point is made. Supplements are not necessarily beneficial—and may be harmful.

# SLEEP STRATEGIES

## Sleep Apnea and Trucking: On the Road to Health and Safety

The American Sleep Apnea Association (ASAA) organized and presented the Sleep Apnea Trucking Conference 2010 (SATC 2010) this May in Baltimore, MD. The conference was cosponsored by the Federal Motor Carrier Safety Administration (FMCSA) and American Trucking Associations (ATA). This day-long program brought together major stakeholders concerned with public policy issues for obstructive sleep apnea (OSA) and the commercial motor vehicle (CMV) driver in an effort to increase awareness, present current programs and research in development, and stimulate forward thinking to work together on this public health issue.

The speakers, and over 400 audience members, included those from governmental agencies (regulatory and advisory), professional truckers (Owner Operator Independent Drivers Association [OOIDA] and major trucking firms), sleep apnea management programs, and the medical community (sleep and occupational medicine). The American College of Chest Physicians (ACCP) was one of many additional supporters. The program was preceded by an evening reception with welcome by Edward Grandi, Executive Director of ASAA, and Mark Berger of Precision Pulmonary Diagnostics. Speakers included Anne Ferro, FMCSA Administrator; Christopher Hart, Vice-Chairman of the National Transportation Safety Board (NTSB); and Jeffrey Burns, Esq., who serves several organizations for improved highway safety, including the Truck Safety Coalition.

### Meeting Highlights

Dr Mary Gunnels (FMCSA Office of Medical Programs) emphasized the large trucking population (400,040 medical examinations monthly) targeted by future regulations. There is increasing awareness of the relationship of obesity and general health concerns, as well as the increase for the risk for OSA. Sleep apnea and sleep disorders are sources for fatigue, and fatigue has been identified as a cause of motor vehicle crashes. The upcoming national registry for medical examiners will include new language and education about sleep apnea.

Dr Martin Walker (FMCSA Chief of Research) reviewed data published May 2002 on the prevalence of OSA in CMV drivers of 28% (17.6% mild, 5.8% moderate, 4.7% severe), with increases noted with age and body mass

index (BMI), as well as 6 or fewer hours of sleep. Severe OSA is associated with increased risk of severe crashes in CMV drivers.

Dr Walker questioned the current status of OSA diagnosis and treatment availability and adherence, and he called for better screening tools, more research on OSA with crash risk, low cost validated testing, determinants of compliance, and better outreach regarding health and safety issues. He presented information about the campaign, "Get on the Road to Better Health: Recognizing the Dangers of Sleep Apnea," by the National Sleep Foundation and FMCSA. He discussed the FMCSA request for proposals for a Commercial Driver Individual Differences Study (CDIDS), studying 21,000 CMV drivers to identify 3,000 cases (crash within the last 3 yr) and 3,000 controls assessing driver factors with high risk for crashes, and a substudy of 1,200 undiagnosed drivers at risk for OSA to undergo testing and treatment to develop a cost effective approach and evaluate linkage to crash risk.

Public health issues, linked to the Department of Health and Human Services Healthy People 2020 ([www.healthypeople.gov/HP2020](http://www.healthypeople.gov/HP2020)), were discussed by Dr Karl Sieber (National Institute for Occupational Safety and Health - NIOSH). He indicated that the increased evaluation for OSA appears to be associated with decreased crashes and stressed importance of monitoring for insufficient sleep. He reviewed a cross-sectional study surveying long haul truck drivers, conducted at 50 truck stops nationally, including health-related scales, such as the Trucker Strain Monitor scale (De Croon et al. *Int Arch Environ Health*. 2001;74[6]: 429-436), a 10-item scale assessing work-related fatigue and sleeping problems. He invited interested members to attend the CD health and wellness conference November 8-10, 2010 ([www.TRB.org/Conferences/HealthWellness2010.aspx](http://www.TRB.org/Conferences/HealthWellness2010.aspx)).

Dr Larry Epstein (Sleep Health Centers Chief Medical Officer) presented the medical overview of OSA symptoms, health risk, diagnosis, and treatment. This raised questions regarding treatment options and compliance from the audience. A common concern, and potential limitation, is the requirement for objective documentation of compliance. At this time, the only OSA treatment that can be objectively monitored is CPAP. Several dental professionals in the audience raised questions about oral appliance treatment. While potentially effective in many people with OSA, the lack of monitoring capability precludes this option for the commercial trucker.

The medicolegal issues, presented by R. Clay Porter, Esq, comprise a large area of concern for truckers, businesses, health-care providers, and government.

Open discussions regarding cases of traffic accidents in the trucking industry and general population focused on liability. Questions that were raised about how to determine when a driver is unsafe to drive addressed the differences in the medical guidelines vs legal requirements in the current language. Issues regarding fatigue risks, inaccuracies in documentation (logs, disclosed medications), and the weight of safety and risk on the driver were discussed. At this time, Department of Transportation disqualification takes priority over guidelines provided by the American Disabilities Act.

Dr Natalie Hartenbaum (Occumedix) brought out one of the group's concerns regarding screening guides. The community has debated whether a

BMI greater than 30 (screen most) vs BMI greater than 33 (screen highest risk) is the better parameter. She also highlighted that medical examiners must consider OSA when evaluating these individuals; that it is not in the driver's best interest, or the public's safety, to look the other way. She, too, discussed CPAP therapy as the current gold standard due to the need for objective compliance. Still unclear is the role of the sleep vs occupational medical provider to sign off on the medical certificate. The "wait period" of 1 month for treatment response raised numerous concerns about patient safety against job/employment security, while Dr Hartenbaum reminded the audience that this was no different than the medical recommendations for the newly diagnosed diabetic or person with coronary artery disease.

Bob Stanton, "just a trucker with sleep apnea" and co-founder of the Truckers with a Cause, a virtual AWAKE group, offered the view as a professional driver and one diagnosed with sleep apnea. While fully supportive of the importance of diagnosis and treatment, he raised a number of unique challenges for even the compliant trucker using CPAP on the road and in the cab of the truck. He also shared his concerns about the risk to livelihood for those without large industry support during initial diagnosis and treatment.

Several representatives from various sleep apnea management programs outlined methods of enhancing availability for diagnosis and treatment for those living on the road. The program concluded with speakers for Schneider National (Don Osterberg) and JB Hunt (Debra Plumlee) who have successfully incorporated such programs into their companies. Raphael Warshaw spoke on behalf of OOIDA and presented the particular challenges facing the individual owner-operator trucker who may not have the safety net of industry support for costs of diagnosis, treatment, and risk to livelihood of out of service time following the diagnosis.

In summary, the association of OSA, fatigue, and crash risk is largely accepted, but its magnitude within the trucking industry and the solution to the problem remain challenged. The Sleep Apnea and Trucking Conference raised many issues regarding sleep and appropriate health care for truck drivers. Who is responsible for clarifying the rules for identification of at-risk truckers? Who will cover the costs of screening programs, diagnosis, and related treatment? Who is responsible for monitoring compliance and ultimate medical clearance? As truck drivers are mobile and can be traveling for weeks at a time, there are unique challenges with access to testing and treatment facilities.

Other acknowledged concerns include limited treatment options with CPAP as the only acceptable noninvasive therapy, documentation of adherence, and guidelines on how much adherence is adequate and the relationship of treatment to improved fatigue and accident risk reduction. How do all of these issues affect the industry-employed vs independent owner-operator trucker? Besides the public health and safety risk issues, there remain individual concerns regarding employment risk. Unfortunately, many of the logistic questions seemed to override the concern for the individual's health and safety.

While there were no major decisions reached, there was general consensus that more dialogue is needed. While the regulatory bodies plan a continued search for objective data for future decision making, there was no response to the audience concerns for current definitive language. The audience was promised a new regulatory document in the making, with a call for better guidelines, more definitive statements, and a clearer path to diagnosis and treatment.

Many voiced the need to "do this again," focusing on sleep-related health of the professional driver (trucker, bus driver, and others with a commercial drivers license). However, with a majority of Americans getting inadequate sleep, drowsy driving issues extend far greater than just sleep apnea in the professional driver, and future policies will hopefully reflect these high-risk health and safety issues. Additional information and links on this topic are available at the official SATC 2010 Web site, [www.satc2010.org](http://www.satc2010.org). ■

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REM Medical, a Sleep HealthCenters®  
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Phoenix, AZ  
and*

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Assistant Professor of Medicine  
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**Dr James Parish, FCCP**  
Section Editor,  
*Sleep Strategies*

## PRESIDENT'S REPORT

# The Power of Partnership

### Background

In the United States, four different national organizations support and represent critical care professionals: 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). Several other professional societies, including the American Society of Anesthesiologists, American Academy of Pediatrics, American College of Emergency Physicians, American College of Surgeons, Society of Hospital Medicine, American Association for the Surgery of Trauma, American Burn Association, American Heart Association, and the Society for Academic Emergency Medicine, have segments devoted to critical care.

The AACN, ACCP, ATS, and SCCM have a combined membership of over 100,000 professionals. Although these organizations all cater to the needs of critical care professionals, there was some competition among the groups

in the past, resulting in duplication of efforts in areas where cooperation would have been preferred. However, in recent years, these organizations



BY DR KALPALATHA K. GUNTUPALLI, FCCP

have established a partnership and an ongoing dialogue, and, consequently, their efforts have been more cooperative and unified.

### What's in a name?

Although the four societies worked together on several issues and projects, their cooperative efforts were not formalized until around the year 2000. The four societies, fondly referred to as

the "quad societies," strove toward a common goal of "societies working together in collaboration for the advancement of critical care." In 2009, the partnership was renamed the "Critical Care Societies Collaborative" (CCSC) to better reflect the spirit of collaboration. Occasionally, one organization may decline to participate on a project if it feels that the issue is not relevant to its members. Sometimes, one organization may independently initiate a project, but the others may then

endorse the project. Ultimately, the CCSC has many accomplishments to its credit that demonstrate the power of partnership.

### How does the collaborative function?

The CCSC members convene at the annual meetings of the SCCM and ACCP. Since the ATS and AACN meetings overlap, traditionally, the CCSC has not met at these meetings.

Since 2008, because of many emerging issues requiring more attention, formal 1- to 2-day retreats have been organized annually. Agenda items that have relevance to the four organizations are identified and discussed in detail at the annual retreat.

### How is this helpful to the membership?

Some of the key achievements and projects resulting from these collaborative efforts, even previous to the formation of the CCSC, are described below:

► **Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS), 2000:** Workforce study conducted by ATS, ACCP, SCCM, and the Association of Pulmonary and Critical Care Medicine Program Directors

pointing out the severe shortage of current and future intensivists and pulmonologists (Angus DC, et al. *JAMA*. 2000;284[21]:2762-2770).

► **Framing Options for Critical Care in the United States (FOCCUS), 2003:**

A task force formed by the AACN, ACCP, ATS, and SCCM discussed how critical care is delivered in the United States and by whom. It provided recommendations addressing the critical care workforce shortage and the quality of critical care delivery (Kelley MA, et al. *Chest*. 2004;125[4]:1514-1517).

► **AACN Standards for Establishing and Sustaining Healthy Work Environments, 2005:** Release of these Standards by the AACN, with endorsement by the other societies.

► **Prioritizing the Organization and Management of Intensive Care Services in the United States (PrOMIS), 2007:** A consensus conference of identified stakeholders of critical care services in the United States was organized to address the perceived problems of and potential solutions for delivery of critical care services (Barnato AE, et al. *Crit Care Med*. 2007;35[4]:1003-1011).

*Continued on following page*

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Continued from previous page

► **Keystone Center, 2008:** The Office of Human Research Protection (OHRP) stopped the Keystone quality improvement initiative in Michigan instituting a checklist to prevent catheter infections, stating that patient consent was necessary. The quad societies wrote a joint letter objecting to this decision, which got a rapid response from the Department of Health and Human Services and led to eventual resolution of the issue. Face-to-face meetings ensued, and position statements were issued by the quad societies.

► **Centers for Medicare & Medicaid Services (CMS) Proposal for Hospital-Acquired Infections:** The quad societies group was invited to contest the CMS proposal for hospital-acquired conditions. The quad societies succeeded in reducing the number of "Never Events" proposed by CMS.

► **Restriction of Duty Hours:** The quad societies responded to the proposed further restriction of house staff duty hours by the ACGME, highlighting the unintended consequences of these regulations.

#### Recent Accomplishments

In 2008, as a result of significant changes in the environment, formal retreats were initiated to allow more dialogue than brief meetings at our

annual conferences allowed. The results of these annual retreats are outlined below.

#### 2008

Agenda items relevant to the four societies were identified. The areas discussed included the following: hospital-acquired infections; patient safety issues; evidence for critical care

### 'THE CRITICAL CARE SOCIETIES COLLABORATIVE HAS MANY ACCOMPLISHMENTS TO ITS CREDIT THAT DEMONSTRATE THE POWER OF PARTNERSHIP.'

practices; new models of care; collaborative opportunities with other organizations, including federal agencies, related organizations, and international professional organizations; and educational joint programs. Along with the National Association for Medical Direction of Respiratory Care (NAMDRC), the Hospital-Acquired Infections Collaborative (HAI-C) was established to address patient safety issues specifically related to hospital-acquired infections.

The Patient Focused Critical Care Enhancement Act – 2007: Drafted by

ACCP and ATS and supported by the CCSC, was introduced in the Senate by Senators Richard Durbin (D-IL) and Mike Crapo (R-ID) and in the House by Representatives Jan Schakowsky (D-IL) and Eric Cantor (R-VA). It was reintroduced in 2009 by Senators Crapo and Sheldon Whitehouse (D-RI) and Representatives Schakowsky and Cantor.

#### 2009

The 2009 retreat resulted in four key accomplishments:

1. A joint open letter to President Obama addressing physician involvement in end-of-life care.
2. Formal name change to the Critical Care Societies Collaborative to more accurately reflect the partnership.
3. A meeting with Dr Don Wright, then the Principal Deputy Assistant Secretary for the Department of Health and Human Services, regarding hospital-acquired infections. In an effort to improve hospital-acquired infection rates, the CCSC submitted three project proposals to HHS, of which one was approved. Currently, with AACN taking the lead, the CCSC is developing a National Awards Program to recognize achievements in the elimination of health-care-associated infections. The CCSC met again with Dr Wright in 2010 to develop further strategies to decrease health-care-associated infections.
4. Decision to share any issues of concern with the collaborative when any society is asked to endorse documents, guidelines, or position papers, or is invited to be part of another entity to partner in areas of common interest. Generally, invitations to collaborate are addressed individually to all of the CCSC organizations from these outside entities.

#### 2010: Current Updates

► **Task Force for Critical Care Research:** Starting in early 2009, the CCSC convened with the NIH US Critical Illness and Injury Trials Group (USCIITG) to develop a comprehensive agenda for critical care research. A multisociety Strategic Planning Task

Force for Critical Care Research was formed whose goal was to define a broad, comprehensive agenda for critical care research. This agenda will serve as a blueprint for future critical care initiatives undertaken by individual investigators and targeted requests for applications issued by foundations, NIH, and other interested groups.

Five areas of research were identified: basic science, clinical, education, translational, and outcomes. The conference document is expected to include a description of the process; an outline of the background information, including research accomplishments and opportunities used by the working groups; and a prioritized list of recommendations for research areas.

► **Tele-ICU Study and Consensus Conference:** A multicenter survey of tele-ICU interventions was performed by the ACCP Critical Care Institute. Subsequently, the Agency for Healthcare Research and Quality funded a conference to develop a consensus statement on the research agenda for ICU telemedicine. This conference was held in March of this year and was attended by an interdisciplinary group representing the four organizations of the CCSC and users/experts of tele-ICUs around the country. The results of this conference will be published as a multisociety consensus statement and will serve to inform potential future requests for applications/proposals on the part of grant-funding agencies. The statement, which is currently being drafted by the writing committee, will be reviewed and approved by all conference participants.

#### Conclusion

Critical care professionals comprise a group of people with diverse backgrounds but with a common goal of improving care of the critically ill patient. By working together through the Critical Care Societies Collaborative, great strides are being made toward that goal. Continued collaboration in the future will lead to even greater accomplishments in the field of critical care. ■

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## This Month in CHEST: Editor's Picks

BY DR RICHARD S. IRWIN, MASTER FCCP

Editor in Chief, CHEST

► **Factors Associated With Illness Perception Among Critically Ill Patients and Surrogates.** By Dr D. Ford, FCCP, et al.

► **Risk of COPD From Exposure to Biomass Smoke: A Metaanalysis.** By Dr G. Hu, et al.

► **Decreasing Cardiac Chamber Sizes**



and Associated Heart Dysfunction in COPD: Role of Hyperinflation. By Dr H. Watz, et al.

#### RECENT ADVANCES IN CHEST MEDICINE

► **Oxygen Therapy for Patients With COPD: Current Evidence and the Long-term Oxygen Treatment Trial.** By

Dr J. K. Stoller, FCCP, et al.

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# Top 5 Things To Do in Vancouver

Looking for ideas on what to do while in Vancouver for CHEST 2010?

How about some recommendations from a local resident? Meet Dr Frank Ervin. Dr Ervin is Clinical Instructor, Department of Medicine, University of British Columbia; and Respiriologist, Ridge Meadows Hospital, Maple Ridge, BC, Canada.

Having lived in Vancouver and Maple Ridge for 23 years, he knows the area well and recently shared recommendations for what to do during your stay in Vancouver.

1. Ride the Skytrain to Surrey on the Expo line, and return via the Millennium line.

The Skytrain offers an area tour for a song, and the system isn't crowded during off-peak hours. Buy a day pass from Translink for the trip. Stop off at the New Westminster Quay "Rivermarket," and walk along the boardwalk, observing the busy river traffic on the Fraser River. I love the New Westminster waterfront area for its vistas and people watching



DR FRANK ERVIN

(www.translink.ca).

2. Take a sightseeing flight on a float plane from the Vancouver Harbor.

You won't believe the beauty of the area from the air, and a float plane experience is great fun in itself

(www.harbourair.com/tours.php).

3. Fly on a float plane to Victoria.

Visit beautiful Victoria, including the Royal British Columbia Museum, or take a side trip to the lovely Butchart Gardens.

Return to Vancouver on the BC Ferries system, and then catch

the Pacific Coach Lines bus on the ferry or in Victoria to return to downtown Vancouver (www.harbourair.com/HA%20Map\_0207.pdf).

4. Spend an evening with the Arts Club Theatre Company. Playing during CHEST 2010 is "The 39 Steps." Hitchcock meets hilarious in this spoof, which features a seductive mystery woman, an accusation



of murder, a missing finger, and a mad dash to foil foreign spies!

Four gifted actors play more than 150 zany characters in this Monty Python-flavored

Hitchcock spoof that just might give you a case of vertigo! (www.artsclub.com/index.html)

5. Listen to the Vancouver Symphony Orchestra.

During CHEST 2010, the Vancouver Symphony Orchestra will present Musically Speaking 1, an evening of music by English composers, including works by Sir Edward Elgar and Ralph Vaughan Williams.

Be sure to buy your tickets online to avoid disappointment! (www.vancouversymphony.ca)

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# Enrollment for EHR Program Available Online

The Centers for Medicare & Medicaid Services (CMS) has established an Internet-based Provider Enrollment, Chain and Ownership System (PECOS) as an alternative to the paper (CMS-855) enrollment process. Internet-based PECOS will allow physicians, nonphysician practitioners, and provider and supplier organizations to enroll, make a change in their Medicare enrollment, view their Medicare enrollment information on file with Medicare, or check on the status of a Medicare enrollment application. The American Recovery and Reinvestment Act of 2009 authorized CMS to provide incentive payments for the "meaningful use" of certified electronic health record (EHR) technology.

For more information about the Internet-based PECOS, select the "Internet-based PECOS" link to the left on the CMS Web site at www.cms.hhs.gov/MedicareProviderSupEnroll; and for additional information, click on "Tips to Facilitate the Medicare Enrollment Process" under "Downloads." If you enrolled in Medicare after November 2003, or have updated Medicare enrollment information since then, you do not need to take further action. To verify your enrollment record in PECOS, go to www.cms.gov/MedicareProviderSupEnroll. ■

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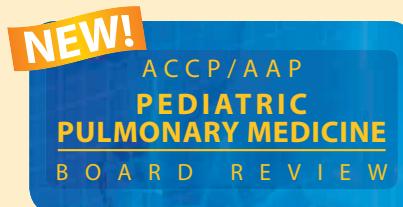
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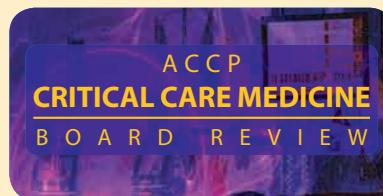


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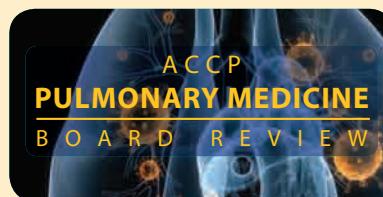
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### ACCP Pulmonary Medicine Board Review 2010

September 1-5  
Orlando, Florida

Exam date: October 12, 2010

## NETWORKS

## CABG, Antibiotic Development, Haiti Challenges, IPF

**Cardiovascular Medicine and Surgery**

The ROOBY trial was a large (2,203 patients), controlled, randomized, multicenter, VA cooperative study that evaluated the efficacy of on-pump vs off-pump coronary artery bypass grafting (CABG). Patients underwent a coronary angiogram at 1 year post-CABG. The main findings were published in the *New England Journal of Medicine* (Shroyer et al. *N Engl J Med.* 2009;361[19]:1827).

The primary short-term composite endpoint included death or major complications (reoperations, cardiac arrest, new mechanical support, stroke, or renal failure requiring dialysis) occurring within 30 days postoperatively or before hospital discharge. The primary long-term composite endpoint was death, nonfatal myocardial infarction, and repeat revascularization within 1 year. Secondary endpoints included completeness of revascularization, graft patency, and neuropsychological outcome.

Short-term primary endpoints for both groups were similar (7% off-pump vs 5% on-pump). Mortality was 1.6% and 1.2% for off-pump and on-pump patients, respectively. As a whole, the off-pump group had a higher long-term primary composite endpoint (9.9% vs 7.4%), more deaths from cardiac causes (2.7% vs 1.3%), higher incomplete revascularization rate (11.1% vs 7.8%), and lower 1-year graft patency (82.6% vs 87.8%) than the on-pump group. The patency for left internal thoracic artery grafted to the left anterior descending artery was similar between the groups (off-pump 95.3% vs on-pump 96.2%). Long-term composite changes in individual neuropsychological test scores were similar or improved from baseline for both groups.

The ROOBY trial is the first large study showing no differences in short-term primary endpoints between the off-pump and on-pump procedures. The long-term endpoint favored the on-pump patients for death or graft patency. The patency rate for internal thoracic artery graft was similar for both groups. No difference in neurocognitive dysfunction was observed between the use of pump and no pump. Both treatment groups showed improvement of neurocognitive function at 1 year.

Dr G. Hossein Almassi, FCCP  
Steering Committee Member

**Chest Infections****Antibiotic Development:****Many Challenges, Few Solutions**

Antibiotic-resistant bacteria are responsible for an increasing number of infections in the hospital and community settings, while the number of antibiotics is decreasing. The Infectious Diseases Society of America (IDSA) has launched "10x20," an initiative to advocate for a global effort to develop 10 new antibiotics by 2020. If this target is not achieved, the IDSA states, "The antibiotic

pipeline problem may change the practice of medicine as we know it."

The reasons behind this dearth of new antibiotics include significant regulatory hurdles, lack of perceived and real value of antibiotics, and lack of accepted clinical markers to establish efficacy of drugs. Dr

The FDA is advocating the development of new diagnostic tests for respiratory antibiotic studies. Sorbello et al (*Drug Inf J.* 2010;44:165) discussed noninferiority (NI) margins for drugs to be used in nosocomial pneumonia (NP). The researchers concluded a 7% NI margin for all-cause mortality in NP (62% placebo estimate; active estimate of 20%) would be adequate. Based on this estimate, 1,500 patients would need to be enrolled in each of two trials for an FDA approval of antibiotics for NP or ventilator-associated pneumonia. Achieving this target would cost more than \$100 million, involve 3,000 patients, and take several years. This may not be reasonable when the IDSA points out that the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) are those that cause nosocomial and other pneumonias (Boucher et al. *Clin Infect Dis.* 2009;48[1]:1).

Meanwhile, the pharmaceutical industry is watching carefully. Though it does not want to turn its back on the crisis, there is little encouragement in 2010 to invest resources to achieve the IDSA's goal for "10x20."

Dr Glenn Tillotson, FCCP  
Steering Committee Member

**Clinical Pulmonary Medicine****Lung Disease in the Elderly**

The US Census Bureau estimates that by 2015, 15% of the US population will be over age 65. As the population ages, it will be important to understand the relationship between aging and lung disease. Dyspnea or dyspnea on exertion is a common complaint of the elderly, but it is also common for older people to attribute dyspnea to the natural process of aging and not report it. It is important for pulmonologists to recognize that dyspnea is underreported and make a special effort to elicit this symptom through patient questionnaires or assessment. Cardiac and respiratory disease are the most common causes of shortness of breath in the elderly and often present as comorbidities, making the diagnosis much more difficult. Studies in normal nonsmoking elderly subjects demonstrate that there is reduced lung elastic recoil, reduced chest wall compliance, and a decrease in respiratory muscle strength. These changes result in a decline in the FEV<sub>1</sub>, the FVC, and the FEV<sub>1</sub>/FVC ratio with aging. The total

lung capacity (TLC) is not changed with age, but the residual volume (RV) does increase, resulting in an increase in the RV to TLC ratio over time. All of these changes can result in the overdiagnosis

of airflow limitation in the elderly. And some research suggests that the elderly are less responsive to bronchodilators.

The symptom of dyspnea must be explored in detail, and lung function studies must be interpreted using "age-ized" lower limits of normal, not percent of predicted.

In the acutely dyspneic elderly, the differential is large and requires a systematic approach to rule out life-threatening cardiopulmonary disorders. Because older patients have multiple comorbidities and there is underreporting of dyspnea by the elderly, these patients present a diagnostic challenge to the pulmonologist.

Dr Craig Piquette, FCCP  
Steering Committee Member

**Disaster Response****Haiti Retrospective**

It has been more than 4 months since my Haitian experience, and I follow the drama there now as the crisis continues. With the *retrospectroscope* on high and with input from many who continue to stay involved in the clinical care on the ground, we can see patterns develop. Specifically, three aspects have emerged that challenge the way forward for the small island country.

► Mass migration and internal displacement of the population. New "cities" now emerge from displaced people who are attempting to set up infrastructure in what were intended as transient camps. The centers have no urban planning, lack basic public health infrastructure, and have rudimentary local governmental control. Such circumstances invite the onslaught of vector, food, and water-borne diseases, as well as violence against the most vulnerable.

► Further decay in the primary health-care capability. Not only did Haiti lose some of its health-care infrastructure, it lost many of its physicians in the earthquake and its aftermath. Many physicians chose to leave after the disaster for more lucrative positions, and many others chose to work for the higher-paying nongovernmental organizations rather than staying in poor rural or community centers. Additionally, reliance on outside health care is developing, which will not likely be sustainable over the years.

► Lack of an integrated, coordinated public health response. Public health programs and vaccine delivery strategies are limited by both supplies and accessibility to the most vulnerable populations. Vaccinations are being fielded by many independent organizations

without a global host nation plan, and coverage is rudimentary, at best.

Given the magnitude of the catastrophe, the vulnerability of the population at baseline, and what has transpired to date, we need to maintain our involvement in the health reconstruction of our island neighbor, Haiti.

Dr Dennis Amundson, FCCP, NetWork Chair

**Interstitial and Diffuse Lung Disease Update in Idiopathic Pulmonary Fibrosis Clinical Trials**

The results of two clinical trials for patients with idiopathic pulmonary fibrosis (IPF) were announced recently.

The first trial, Bosentan Use in Interstitial Lung Disease (BUILD)-3, enrolled 616 patients with biopsy-proven IPF in a randomized, double-blind, placebo-controlled study. Patients received bosentan (n=407), a dual endothelin receptor antagonist, or placebo (n=209) over a 52-week period. The primary endpoint was time to progression of disease or death. Secondary endpoints included quality-of-life measures and change in pulmonary function studies.

Investigators found no significant differences between groups with respect to the primary or secondary endpoints. Subgroup analyses similarly failed to achieve the prespecified endpoints. Patients receiving bosentan had a significantly increased rate of elevated liver function study results compared with the placebo group. The investigators concluded that bosentan was no different than placebo in this trial.

The second study was a randomized, double-blind, placebo-controlled study of 180 patients with advanced IPF. See the report on p. 3 of this issue for more details.

Two additional clinical trials, sponsored by the NHLBI-funded IPF Clinical Research Network, are now enrolling patients. PANTHER-IPF (ClinicalTrials.gov identifier NCT00650091) is a randomized, double-blind study evaluating prednisone vs azathioprine, and N-acetylcysteine vs N-acetylcysteine vs placebo in IPF, while ACE-IPF (ClinicalTrials.gov identifier NCT00957242) is examining the efficacy of anticoagulation with warfarin vs placebo in patients with IPF.

Dr Imre Noth, FCCP, NetWork Chair; and  
Dr Eric S. White, FCCP, NetWork Member

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## Darlene Buczak Award for Innovations in Education

BY DR BRIAN CARLIN, FCCP

The Darlene Buczak Award for Innovations in Education was established by the Association of Pulmonary and Critical Care Medicine Program Directors in 2009 to honor Ms. Buczak's service to the organization. This award is given to an individual who demonstrates excellence and innovation in the education of pulmonary and critical care medicine fellows. The award is given on a yearly basis.

Dr Jennifer McCallister, Associate Fellowship Director for the Ohio State University pulmonary and critical care medicine training program, was the first recipient of the award. Dr McCallister has developed a month-long immersion curriculum that is delivered to all incoming first-year fellows during the month of July. This curriculum is designed to establish minimum cognitive and procedural competencies in key topics and procedures in the field prior to the new fellow beginning actual patient care responsibilities.

In the program, lectures and computer-based lessons are used to review relevant basic physiology, core clinical topics, and essential procedures. Technical skills and baseline procedural competencies are established through the use of simulators, cadaver laboratories, direct faculty



(L-R) Dr John Buckley, FCCP; Dr Jennifer McCallister; Darlene Buczak; Dr Laura Evans; Dr John Mastronarde; and Dr Brian Carlin, FCCP.

instruction, and wet labs. Competency is assessed through a written pretest and posttest and direct observation of skills by faculty members. The curriculum is in its third year and has been well received by both fellows and faculty.

Dr Laura Evans, Associate Fellowship Director for the New York University pulmonary and critical care medicine training program, was this year's recipient of the award. Dr Evans has developed a structured research curriculum for fellows in an attempt to improve the career development process. This curriculum has been in place for the last 2 years and is started

during the first year of the training program.

First-year fellows attend a 2-day "research retreat" to learn about ongoing research activities, meet the research faculty, and receive an overview of possible pathways toward an academic career. Each fellow is then expected to meet with potential research mentors over the ensuing months and to choose a research project. At the beginning of their second year in training, a series of research

methodology lecture courses is given. The curriculum has been perceived to be beneficial from both the faculty and fellow perspectives.

Assessment of competency of cognitive and procedural skills and development of clinician scientists are just two of many aspects of training that are essential to the education of pulmonary and critical care fellows. Drs. McCallister and Evans have developed innovative methods to address these two issues, with positive outcomes. These two projects show the innovations in education and training that form the basis for the Darlene Buczak award. ■

## College VP Receives CME Award

Ed Dellert, ACCP Vice President of Clinical Education, Informatics, and Research, is the recipient of the Research in Continuing Medical Education (RICME) Award from the Society for Academic Continuing Medical Education (SACME). Melinda Steele, MEd, SACME Past President, made the presentation, and ACCP President, Dr Kay Guntupalli, FCCP, represented the ACCP at the event this past April. The award honors those who have made outstanding contributions to research in continuing medical education.

SACME was established in 1976 as the Society of Medical College Directors of Continuing Medical Education (SMCDCME). In 1998, SMCDCME was renamed the Society for Academic Continuing Medical Education (SACME). Its mission is to promote the research, scholarship, evaluation, and development of CME/CPD (continuing medical education/continuing professional development) that helps to enhance the performance of physicians and other health-care professionals practicing in the United States, Canada, and elsewhere for purposes of improving individual and population health. ■

## 3rd Annual Case Competition Addressed Diabetes

The CHEST Foundation, the philanthropic arm of the American College of Chest Physicians (ACCP); the Social Enterprise at Kellogg (SEEK) of the Kellogg School of Management; the Carol and Larry Levy Social Entrepreneurship Lab; and Medtronic Diabetes sponsored the 3rd Annual Case Competition that held its culmination dinner on May 11, 2010. Partners of this year's competition included the Centers for Disease Control and Prevention (CDC) Foundation and the American Diabetes Association (ADA).

The 2010 case competition addressed the growing epidemic of diabetes in the United States. Professor Timothy Feddersen, Wendell Hobbs Professor of Managerial Politics and Director of SEEK, Kellogg School of Management, and Jamie N. Jones, PhD, Assistant Director of Social Enterprise and the Carol and Larry Levy Social Entrepreneurship Lab at Kellogg, challenged the teams to devise viable business models that would link care providers, patients, and community resources in the successful treatment of diabetes. Six student teams from

the Kellogg School of Management and the Feinberg School of Medicine developed sustainable business solutions that focused on providing innovative diabetes care models.

As in the previous 2 years, the case competition secured the expert assistance of members of the medical, community, and business realms to work as advisors with the six competing teams. National leaders from the business, government, and philanthropic sectors served as preliminary reviewers and final judges.

This year's preliminary judges were Dr John C. Alexander Jr, FCCP, President, The CHEST Foundation, and Head of Cardiac Surgery, NorthShore University Health System; Robert F. Barnett III, Board Member, The CHEST Foundation, and Financial Advisor, WexCap Advisors; Jeffrey C. Bauer, PhD, Partner, Management Consulting-Futures Practice, ACS Healthcare Solutions; David Dranove, Walter J. McNerney Professor of Health Industry Management and Director of Health Enterprise Management at Kellogg; Professor Tim Feddersen;



Professor Tim Feddersen and Dr John Alexander pose with the 2010 Kellogg Case Competition winning team, Dia-life. Team members (L-R): Harold Hsiung, Ajit Thupil, Mihir Naware, Amy Ide, Milind Kopikare, and Will Liu.

Dr Allen I. Goldberg, Master FCCP, Past President, ACCP; Jamie N. Jones, PhD; Marilyn A. Lederer, CPA, Executive Director, The CHEST Foundation; and Sangeeta Vohra, Associate Director of The Center for Biotechnology at Kellogg. These judges reviewed the six cases to determine which two teams would present to the distinguished panel of judges at the culmination dinner.

Final round judges included Christine Beebe, Associate Direc-

tor, Takeda Pharmaceuticals North America, Inc, and Incoming-Chair of the Board for the ADA-Chicago Chapter; Thomas Haggerty, President, Institute of Allied Medical Professions; Greg Kapust, CEO, Breathe Technologies; Rachel Lieberman, Director of Programs, ADA-Chicago Chapter; John Moore, PhD, RN, Chronic Disease Director's Office, CDC; and Leo Mullin, Chairman of the Board, Juvenile Diabetes Research Fund, and Senior Advisor,

Goldman Sachs Capital Partners.

The two finalist teams—Ticket To Change and Dia-life—presented their business plans at the dinner. Dia-life team members Harold Hsiung, Will Liu, Milind Kopikare, Amy Ide, Mihir Naware, and Ajit Thupil developed the winning plan, which focused on assisting patients with the necessary lifestyle changes required to effectively manage diabetes. They created an online system of tangible incentives for patients that encourages and supports lifestyle changes.

The runner-up team, Ticket To Change, included student team members Mitra Afshari, Avidan Ben Har, Josh Engel, Frank Sasso, Bill Shields, and Timmie Wang. They presented their plan that encompassed behavioral change interventions known to be helpful in the health of those diagnosed with diabetes, including education, support, lifestyle changes, and participant incentives, which will improve key health metrics.

For more information about the Kellogg/CHEST Foundation collaboration, visit the Foundation's Web site at [www.chestfoundation.org](http://www.chestfoundation.org). ■

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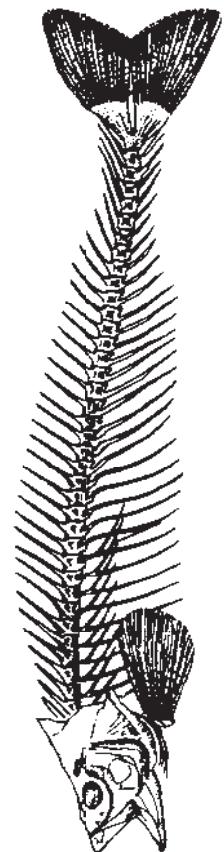
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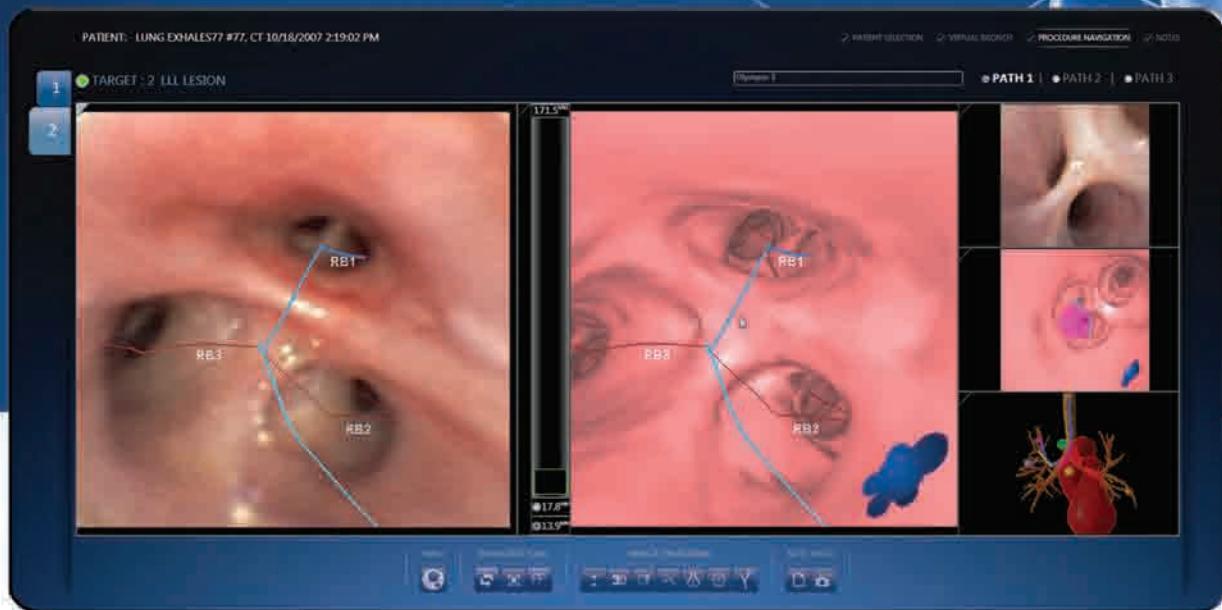
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