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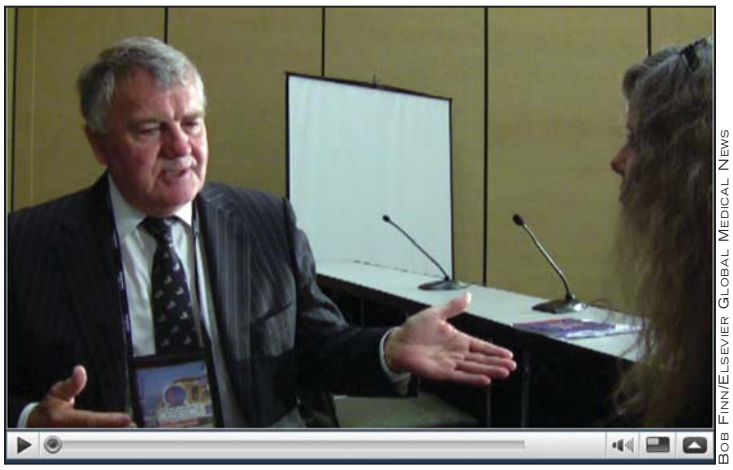

BOB FINN/ELSEVIER GLOBAL MEDICAL NEWS

One in six lung cancer patients are expected to receive a different staging category based on the new edition of the TNM staging system, explained Dr. Peter Goldstraw.

New Lung Cancer Staging System Debuts

BY BETSY BATES
Elsevier Global Medical News

SAN FRANCISCO — A revolutionary new staging system for lung cancer will profoundly impact treatment decisions and patients' eligibility for clinical trials, even as it unites clinicians from disparate specialties and nations in characterizing tumors, node involvement, and metastasis.

Fully one in six lung cancer patients will receive a different staging category based on the just-released 7th edition of the TNM staging system, reported Dr. Peter Goldstraw, chair of the staging project of the International Association for the Study of Lung Cancer (IASLC), at the association's World Conference on Lung Cancer.

"Some of these patients, if not the majority of these patients, will therefore be considered for different modalities of care, and—commonly now, of course—multimodality care," said Dr. Goldstraw, consultant and professor of thoracic surgery at Royal Brompton Hospital in London, at a plenary session during the meeting.

The revisions to the TNM (tumor, node, metastases) system are based on multidisciplinary contributions from the world lung cancer community, drawing on data compiled from more than 100,000 lung cancer cases from 46 centers in 19 countries. The IASLC led the revision effort, but both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have accepted the recommendations.

"This represents the first real change [in staging] for the last 20 years [and a] radical departure from the past," said Dr. Goldstraw during a press conference.

In the past, staging classifications were dictated by a small panel of experts, mostly surgeons, and were based on limited numbers of mostly surgical patients, he explained, "which created a great deal of

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Experts Outline Therapy for H1N1, Seasonal Flu

First-line antivirals vary by flu strain.

BY BRUCE JANCIN
Elsevier Global Medical News

VAIL, COLO. — The recommended antiviral therapy during the coming influenza season will depend on whether a patient has laboratory-confirmed novel influenza A(H1N1).

In patients with confirmed novel influenza A(H1N1), or in patients with laboratory-confirmed influenza A(H3N2) or B, the first-line antiviral is oseltamivir (Tamiflu). However, in patients with a positive laboratory test for influenza A or seasonal A(H1N1), the preferred agent is zanamivir (Relenza), according to Centers for Disease Control and Prevention recommendations based on antiviral resistance patterns.

Zanamivir is also the first-line agent in patients who are suspected of having influenza on clinical grounds but who did not have laboratory tests or had negative results, Dr. Adriana Weinberg explained at a conference on pediatric infectious diseases sponsored by the Children's Hospital in Denver.

Novel H1N1, A(H3N2), and B viruses share the same antiviral susceptibility pattern—all are susceptible to both zanamivir and oseltamivir. However, oseltamivir is preferred because as an oral agent it is easier to administer than the inhalation powder zanamivir, has fewer side effects, and is approved for use across a wider age range, added Dr. Weinberg, professor of pediatrics and medicine and medical director of the clinical virology laboratory at University of Colorado Hospital, Anschutz.

The recommended alternative to zanamivir in patients with laboratory evidence of influenza A, a negative test result,

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Compliance Cuts ICU Infection Rates

BY SUSAN BIRK
Elsevier Global Medical News

CHICAGO — Bundles of interventions aimed at reducing ventilator-assisted pneumonia and central line bloodstream infections in intensive care units significantly lowered infection rates only when all of the components were implemented correctly, according to a survey of hospitals participating in the National Healthcare Safety Network of the Centers for Disease Control and Prevention.

The findings have implications for the development of recommendations and mandatory reporting requirements for hospitals, said Patricia Stone, Ph.D., of the Columbia University School of Nursing, New York, in a poster at the annual research meeting of AcademyHealth. "Policy makers must consider that different settings may have different problems," she said. Reporting requirements are time consuming and could potentially hinder hospitals' efforts to zero in on the

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Oseltamivir Resistance Feared

Flu • *from page 1*

or no testing is the combination of oseltamivir plus rimantadine (Flumadine). For patients who are positive for seasonal influenza A(H1N1), the fallback antiviral regimen is rimantadine alone.

Alternatives to the inhalation-only zanamivir are important, because that administration route is problematic in patients who are intubated or have asthma or other airway disease. Plus, zanamivir isn't approved for use in children younger than age 7 years, she noted.

In contrast, on April 28 the Food and Drug Administration approved a 1-year Emergency Use Authorization for the use of oseltamivir for treatment and prophylaxis in infants.

A big concern among virologists and infectious disease specialists, according to Dr. Weinberg, is that the novel H1N1 virus will become resistant to oseltamivir, as did seasonal A(H1N1). This could occur if the novel H1N1 in a patient coinfected with seasonal A(H1N1)—a not-uncommon scenario—acquired the oseltamivir-resistance mutation.

"Then we have the possibility of creating a true monster," Dr. Weinberg said.

To date, three cases of oseltamivir-resistant novel H1N1 have been reported to the World Health Organization. But in addition to the emergence of resistance, there is also a phenomenon known as regression of resistance, which works in favor of public health. For example, influenza A(H3N2) in Japan went from 100% oseltamivir resistant during the 2005-2006 season to 78% resistant the next year.

Numerous investigational antiviral agents are well along in clinical trials. One that could prove particularly valuable is an intravenous formulation of zanamivir, a drug still active against all strains of influenza. Another promising drug is peramivir, a neuraminidase inhibitor that appears to be effective and well tolerated.

"Peramivir has the same resistance pattern as oseltamivir. Its big advantage is it can be administered parenterally. That's going to be really important in patients with severe influenza, in whom oral drugs aren't going to be reliable," Dr. Weinberg noted.

Ribavirin and several interferons that are already commercially available for other indications are known to have some activity against influenza. The use of these drugs is being better defined in ongoing clinical trials.

In severe influenza that's not responding to recommended treatment, combination therapy with neuraminidase inhibitors, adamantanes, interferon, and ribavirin will be appropriate. "It's going to be trial and error, basically," Dr. Weinberg said. ■

Dr. Mark Metersky, FCCP, comments: *It remains unclear how much that is true now about the novel H1N1 pandemic will remain true when (or if) the pandemic reasserts itself in the United States this fall. Underscoring the dynamic nature of the pandemic is a recent report of two cases of oseltamivir-resistant H1N1 in the United States.*

IN THIS ISSUE

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Device May Detect Lung Cancer Cells in Sputum

BY ROBERT FINN
Elsevier Global Medical News

SAN FRANCISCO — An investigational device could make sputum screening a routine part of health examinations in patients at risk for lung cancer, its developers suggested at the World Conference on Lung Cancer.

The Lung Cell Evaluation Device (LuCED) can discriminate normal cells from cancerous cells in sputum with 90% sensitivity and near 100% specificity, according to its manufacturer, VisionGate Inc.

LuCED is currently available as a research instrument. Dr. Robert Honigberg, VisionGate's consulting chief medical officer, said that the company hopes to receive Food and Drug Administration approval for a noncancer indication—the detection of macrophages in gastroesophageal reflux disease—by 2010, with approval of a lung cancer indication targeted for 2011.

Company officials discussed the device at a press briefing on innovative diagnostics organized by the International Association for the Study of Lung Cancer, which sponsored the conference.

LuCED is based on a patented technology called Cell-CT, which uses light microscopy to assemble highly detailed three-dimensional images of individual cells as they rotate in a capillary tube. The software then quantifies critical morphological features to discriminate normal cells from cancerous ones.

The results are entered into a proprietary formula to produce a "LuCED Score" that differentiates cancer cells from normal cells, and also classifies different types of cancerous cells. Higher scores would signal the presence of cancer cells.

"We can get very close to 100% accuracy for normal sputum, and about 90% accuracy on sputum with cancer cells," said Michael Meyer, VisionGate's vice president for image engineering, who presented the company's study. "The score gives us a basis upon which we can proceed with triage."

In one scenario, he suggested, patients in a high-risk category might be screened at annual intervals. Those with precancerous cells would be subject to increased surveillance, whereas those with cancerous cells would receive additional diagnostic tests such as bronchoscopy and diagnostic CT.

About 75% of sputum samples from people with cancer contain abnormal cells, according to Mr. Meyer. These cells constitute only a small minority of the cells in sputum, however, which makes automated analysis challenging. In addition, the cells are trapped in a matrix of mucus, where they are often massed in large clusters of varied kinds of cells.

The first step in the analysis involves processing the specimen to dissolve some of the mucus. An immunomagnetic separation process removes a large number of the normal cells, and the specimen is further processed to break up some of the clusters. Individual cells are then introduced into a capillary tube one by one. As the tube rotates, the light microscope obtains images from many angles. When the device is fully developed, the examination of about 1,000 cells is expected to take about 20 minutes. ■

Dr. W. Michael Alberts, FCCP, comments: *This is a promising screening technique. The report of very high sensitivity and specificity, however, will need to be confirmed, especially in real-world settings.*

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Protective Options Abound Against H1N1 Influenza

Hospitals must decide which measures to use to contain the spread of pandemic flu.

BY HEIDI SPLETE
Elsevier Global Medical News

As hospitals prepare for a potential surge in cases of the pandemic influenza A(H1N1) virus this fall, physicians must make decisions about protective measures based on limited evidence about the virus's transmission and severity.

Planning for H1N1 influenza includes everything from ordering extra surgical masks to providing family support for hospital staff so they can come to work, said Leonard Mermel, D.O., professor of medicine at Brown University and medical director of the department of epidemiology and infection control at Rhode Island Hospital, both in Providence, R.I.

Dr. Mermel said that during the first wave of H1N1 influenza last spring, he had "rather draconian measures" in place, based on data from Mexico suggesting a high mortality rate. "I had a triage desk in our [emergency department], and N95 respirators," he said in an interview.

But conversations with colleagues, resistance from his staff to routine N95 use, and emerging signs that the new virus was behaving like the seasonal flu virus led to a transition to standard droplet precautions, said Dr. Mermel, who was part of a panel discussion on infection control measures at an Institute of Medicine–sponsored workshop on the use of personal protective equipment for health care workers.

Dr. Mermel meets regularly with a working group at Rhode Island Hospital to discuss infection control procedures. Their plans for responding to H1N1 influenza include "cough etiquette stations" with surgical masks, hand hygiene products and instructions for their use at hospital points of entry, and a triage desk where a staff person will remind people to follow the instructions.

Other potential strategies to prevent H1N1 virus transmission include limiting unnecessary visitors to the hospital, limiting procedures that might increase the risk of virus transmission, and assigning immunized personnel to perform such procedures, Dr. Mermel said.

As for personal protective equipment, "it's a real hornet's nest," he said. The Centers for Disease Control and Prevention recommends the use of N95 respirators by health care workers who are treating patients with novel H1N1, but the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and other organizations have concluded that standard droplet precautions are probably sufficient.

"At this moment, we are using droplet precautions for standard care and [N95] respirators for aerosol-generating procedures," Dr. Mermel said.

"It's of great importance to mitigate transmission from health care worker to health care worker," he added. A worker could do everything right in terms of personal protective equipment, and then become infected during a lunch break with a colleague who is coughing.

Dr. Mermel's working group has been coordinating with the human resources department to reinforce the message that staff should stay home when ill. But the working group also has considered how to help healthy health care workers get to work if they need child care or elder care at home.

An especially tricky question is whether to reassign health care workers who may be at high risk for H1N1 infection, such as pregnant women, Dr. Mermel said. The CDC recommends reassigning high-risk health care workers, but recent statements from the SHEA and the IDSA cite problems with that approach.

The CDC may change its guidance on protective measures after reviewing the IOM panel's report. If the CDC maintains its recommendations, hospitals will have to decide how far to follow them, Dr. Mermel said. ■

Diagnostic Challenges Anticipated In Pandemic H1N1 Influenza

BY BRUCE JANCIN
Elsevier Global Medical News

VAIL, COLO. — Recent anecdotal reports suggest that the diagnosis of pandemic influenza A(H1N1) virus should not be ruled out by a negative upper respiratory tract specimen in a patient with pneumonia.

There have been two patients at Albany (N.Y.) Medical Center and one in Denver who were hospitalized with severe lower respiratory tract infections whose nasopharyngeal swabs were negative for influenza A by rapid tests—but who had endotracheal aspirates positive for the H1N1 virus by culture and polymerase chain reaction.

"That's something to watch for. It would be consistent with findings in animal models showing the virus replicates very well in the lower respiratory tract," said Dr. Adriana Weinberg, who reported on the cases at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

"As the pandemic evolves, perhaps we may see more cases with florid infection in the lower respiratory tract," said Dr. Weinberg, professor of medicine, pediatrics, and pathology and medical director of the clinical virology laboratory at the University of Colorado Hospital, Aurora.

At present, the preferred specimens for making the diagnosis of pandemic influenza are the same as for seasonal influenza: nasal washings in children and nasopharyngeal aspirates or swabs in adults. That being said, negative results on those upper respiratory tract specimens do not necessarily rule out pandemic influenza in patients with lower respiratory tract infections.

"In these patients, you may want to proceed with obtaining an induced sputum, an endotracheal aspirate, or a bronchoalveolar lavage specimen to rule out the pandemic strain," said Dr. Weinberg.

Most diagnostic tests for seasonal influenza A or A plus B will also pick up the pandemic strain. One caveat is that the rapid tests, which in general are not terribly sensitive for the diagnosis of seasonal influenza viruses, appear to be even less sensitive for pandemic influenza. " However, culture and PCR [polymerase chain reaction] are extremely sensitive" for the pandemic strain, she continued.

'As the pandemic evolves, perhaps we may see more cases with florid infection in the lower respiratory tract.'

DR. WEINBERG

The Centers for Disease Control and Prevention has acted quickly in preparing tools for the diagnosis of H1N1 influenza. Regular PCR and culture cannot differentiate between seasonal influenza and the pandemic H1N1 influenza strain. But just 2 weeks after the first U.S. case of H1N1 influenza was diagnosed in April, the CDC began sending out to U.S. sentinel laboratories PCR kits that are highly specific for the virus. Less than 2 months later, those kits were on-site at all state health department laboratories, and at 386 international laboratories.

In addition to many more patients with H1N1 influenza presenting with lower respiratory tract infection, physicians can expect to see lots more patients with a prominent GI presentation. Animal studies suggest that the pandemic strain replicates much better in the GI tract than do seasonal influenza viruses, and that has been borne out in the first 400 U.S. cases of H1N1 influenza.

More than 90% of those patients presented with fever and cough, and two-thirds had a sore throat—all typical of seasonal influenza—but in addition, 25% presented with diarrhea and 25% had vomiting. ■

WHO Panel: Make Health Workers Top Priority for Pandemic Vaccine

BY JONATHAN GARDNER
Elsevier Global Medical News

Health care workers should be the top priority to receive immunization with the pandemic influenza vaccine, and individual countries should take their nations' domestic needs into account when determining how to prioritize inoculating subgroups vulnerable to the virus, a top international health panel has decided.

The World Health Organization's Strategic Advisory Group of Experts on Immunization has said that vaccinating health care workers is necessary to maintain a functioning health care system and prevent infection with the pandemic influenza A(H1N1) virus in people who have preexisting illnesses, Dr. Marie-Paule Kieny, director of WHO's initiative for vaccine research, said in a press teleconference.

Countries are advised to prioritize the vaccination of such vulnerable groups as the chronically ill and children depending on each country's domestic needs, Dr. Kieny said. Thus, countries whose first priority is reducing sickness and death may choose to focus on inoculating the elderly and chronically ill first, whereas those countries whose priority is reducing the spread of infection may decide to inoculate schoolchildren first, she said.

The expert panel made its recommendations after a meeting the week of July 6. WHO Director-General Dr. Margaret Chan endorsed the recommendations July 11.

The panel also concluded that at this time there is no concern regarding the safety of the tested pandemic influenza vaccine, but there is still an "urgent need" to collect more safety data on subgroups, Dr. Kieny said. New adjuvants are being used in some pandemic vaccines that have not been fully tested, so postmarketing surveillance must also be effective, according to the panel.

In addition, the panel said data on immunogenicity and postmarketing safety and surveillance studies need to be shared among the countries to allow for adjustments in immunization policy, she said.

The panel added that Northern Hemisphere countries should proceed with plans for seasonal influenza vaccination as if there were no pandemic, because production of the seasonal vaccine is almost complete, she added. ■

EGFR Inhibitors Useful in Subset of NSCLC Patients

Women, nonsmokers, and former light smokers were among those more likely to carry EGFR mutations.

BY MARY ANN MOON
Elsevier Global Medical News

Two inhibitors of the epidermal growth factor receptor tyrosine kinase—gefitinib and erlotinib—were effective for patients with non–small cell lung cancer who carried mutations of the EGFR gene, according to separate phase III clinical trials published online in the New England Journal of Medicine.

The populations most likely to carry the EGFR mutations are women, patients who have never smoked or who formerly were light smokers, patients with pulmonary adenocarcinomas rather than other lesions, and patients of Asian ethnic background.

In one of the studies, patients with EGFR mutations who were treated with gefitinib had "a remarkably high objective response rate (71%) and prolonged progression-free survival," the researchers noted. In the other study, "the overall rate of complete or partial response to erlotinib was 70%" among carriers of EGFR mutations, the investigators said.

In both studies, the toxic effects of therapy were modest and well tolerated, the authors noted.

In the first study, Dr. Tony S. Mok of Chinese University of Hong Kong and his associates compared first-line treatment with oral gefitinib against standard combined carboplatin-paclitaxel therapy in an open-label fashion among 1,217 patients at 87 medical centers in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, and Thailand. The study subjects had stage IIIB or IV NSCLC with histologic features of adenocarcinoma and were nonsmokers or former light smokers.

The study was sponsored and supervised by AstraZeneca PLC.

The median progression-free survival was 5.7 months with gefitinib and 5.8 months with carboplatin-paclitaxel. One-year rates of progression-free survival were 24.9% and 6.7%, respectively. Thus, gefitinib demonstrated noninferiority or superiority to standard therapy, the investigators noted.

In the overall study population, the objective response rate was significantly higher with gefitinib (43%) than with carboplatin-paclitaxel (32%). But the difference was much more striking in the subgroup of 261 patients who carried EGFR mutations: Their objective response rates were 71.2% with gefitinib and 47.3% with carboplatin-paclitaxel.

PATIENTS WITH EGFR MUTATIONS HAD 'A REMARKABLY HIGH OBJECTIVE RESPONSE RATE (71%)' WHEN TREATED WITH GEFITINIB.

In dramatic contrast, among patients who did not carry EGFR mutations, "the objective response rate with gefitinib was 1.1%, and progression-free survival favored chemotherapy," Dr. Mok and his colleagues said (N. Engl. J. Med. 2009 [doi:10.1056/NEJMoa0810699]).

However, overall survival did not differ significantly between the two groups, at 18.6 months with gefitinib and 17.3 months with carboplatin-paclitaxel.

"Overall survival, perhaps the most important end point of cancer treatment, was not improved by gefitinib, for reasons not discussed by the authors," Dr. Adi F. Gazdar of the University of South Texas Medical Center, Dallas, noted in an editorial comment accompanying the report.

"Several questions remain to be answered before we can extrapolate the results" of this study of Asian patients to other populations, Dr. Gazdar said, but the findings do suggest that first-line tyrosine kinase therapy should be considered for carefully selected subgroups of patients (N. Engl. J. Med. 2009 [doi:10.1056/NEJMe0905763]).

The rate of grade 3 or 4 adverse effects was lower with gefitinib (29%) than with standard chemotherapy (61%), as was the rate of adverse effects leading to discontinuation of therapy (7% and 14%, respectively) and the rate of dose modification because of toxicity (16% and 35%, respectively). The rate of serious events including death was approximately 16% in both groups.

"The incidences of rash or acne, diarrhea, and elevated liver aminotransferase levels were significantly higher with gefitinib than with carboplatin-paclitaxel, whereas the incidences of neurotoxic effects, nausea and vomiting, and hematologic toxic effects were significantly higher with carboplatin-paclitaxel," Dr. Mok and his colleagues said.

"Our findings suggest that, whenever possible, EGFR-mutation status should be determined before the initial treatment of pulmonary adenocarcinoma," they added.

The second NSCLC study demonstrated that large-scale screening of a Western patient population for EGFR mutations is not only feasible but also warranted, its authors said, because it could lead to customized treatment with erlotinib and improved outcomes.

In the study, 2,105 patients from 129 medical centers across Spain were prospectively screened for EGFR mutations. All had stage IIIB disease with pleural effusion or stage IV NSCLC. The median time required for the genetic analysis was 7 days.

Mutations were found in samples from 350 patients (17%). They were more common among women (70%), patients who had never smoked (67%), and patients with adenocarcinomas (81%), said Dr. Rafael Rosell of the Catalan Institute of Oncology, Badalona, and his associates.

A total of 197 of the patients with EGFR mutations received erlotinib and were available for evaluation. After a median follow-up of 14 months (range, 1-42 months), 24 patients had a complete response, 115 patients had a partial response, 38 patients had stable disease, and 20 patients had progressive disease.

The overall rate of objective response among the carriers of EGFR mutations was 70.6%, almost exactly the rate with gefitinib in the study by Dr. Mok and his colleagues.

"Overall, median progression-free survival … was 14 months, and median overall survival was 27 months, which is an improvement over findings in patients with lung cancer that have been reported previously," Dr. Rosell and his colleagues said (N. Engl. J. Med. 2009 [doi:10.1056/NEJMoa0904554]).

The most common adverse events with erlotinib were rash and diarrhea, and no patient withdrew from the study because of toxicity.

Dr. Mok reported receiving consulting fees from F. Hoffmann-La Roche Ltd., AstraZeneca, Pfizer Inc., and Eli Lilly & Co., as well as lecture fees from Roche, AstraZeneca, and Eli Lilly. Dr. Gazdar reported receiving consulting fees from AstraZeneca, Genentech Inc., and Boehringer Ingelheim GmbH. Dr. Rosell reported no financial conflicts of interest. His study was supported by the Spanish Ministry of Science and Innovation, the La Fundación Badalona Contra el Cáncer, and the Bonnie J. Addario Lung Cancer Foundation. ■

Dr. W. Michael Alberts, FCCP, comments: *These studies suggest that EGFR-mutation status may provide guidance for the initial treatment of patients with advanced stage adenocarcinoma of the lung.*

Difficult to Control Asthma May Be Vocal Cord Dysfunction

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — About one-third of patients referred to an asthma specialty clinic who were believed to have difficult to control asthma actually had vocal cord dysfunction, results from a single-center study showed.

"If patients have been on many different medicines—they've been on oral or inhaled steroids and they're not responding—it's worth checking to see if they actually have asthma or not," study coauthor Catherine Vitari, R.N., said in an interview during a poster session at an international conference of the American Thoracic Society.

In a study led by her associate, Dr. Sally E. Wenzel, FCCP, a pulmonologist and the director of the Asthma Institute at the University of Pittsburgh Medical Center, the researchers reviewed the charts of 152 new patients who were evaluated at the institute between December 2006 and September 2008 in an effort to verify if the diagnosis of severe asthma was substantiated or not.

Of the 152 patients, 119 (78%) had a presenting diagnosis of asthma while 33 had another diagnosis such as dyspnea, cough, and emphysema.

All patients underwent a full evaluation.

Ms. Vitari, a clinical research nurse at the Asthma Institute, reported that 40 of the 119 patients who presented with an asthma diagnosis underwent methacholine challenges with laryngoscopy because their history and physical suggested asthma may not be the primary diagnosis. Of the 40 patients, 39 had a negative test, which precluded the diagnosis of asthma in 33% of the 119 patients.

'IF PATIENTS HAVE BEEN ON MANY DIFFERENT MEDICINES … IT'S WORTH CHECKING TO SEE IF THEY ACTUALLY HAVE ASTHMA OR NOT.'

"We didn't expect to see this," Ms. Vitari commented. "That's a pretty high percentage of people referred for asthma who didn't actually have asthma."

She also noted that four of seven patients who presented with a diagnosis of cough, which may indicate asthma, had methacholine challenges with laryngoscopy that showed vocal cord dysfunction; the three other patients were diagnosed with vocal cord dysfunction based on their exam and testing.

Ms. Vitari noted that it's Dr. Wenzel's practice to perform a laryngoscopy at the time of the methacholine challenge "to see if the vocal cords are closing or spasming, indicating vocal cord dysfunction, or if it's truly asthma," she explained. "If you think it's vocal cord dysfunction and you send the patient to ENT instead to do a laryngoscopy and they don't see anything, it could be that the vocal cord dysfunction isn't acting up at that time since the spasms can be episodic and/or related to triggering events/stimuli."

She acknowledged certain limitations of the study include its single center design and the fact that only one physician did the assessments.

The researchers had no conflicts to disclose. ■

Pages 4a—4b

Easy Quitting by Heavy Smokers May Be Red Flag

BY BETSY BATES
Elsevier Global Medical News

SAN FRANCISCO — An unusual pattern of sudden, effortless smoking cessation in long-term smokers may herald the onset of lung cancer in a small subgroup of patients, researchers reported at the World Conference on Lung Cancer.

It has been well documented that lung cancer patients often stop smoking shortly before their diagnosis, with the assumption that symptoms such as shortness of breath, coughing, or pain create a strong motivation for behavior change.

Now a pilot study suggests that in certain lung cancer patients—even some with long-term smoking histories and significant levels of nicotine addiction—smoking cessation occurs in the absence of symptoms or even a focused effort to quit.

"This has led us to speculate that in some cases, spontaneous smoking cessation may be a presenting feature of lung cancer, possibly caused by tumor secretion of a factor interfering with nicotine addiction," said Dr. Barbara Campling, a medical oncologist with the University of Pennsylvania in Philadelphia.

In a study conducted at the Philadelphia VA Medical Center, 115 smokers and former smokers diagnosed with lung cancer were compared to 101 smokers and former smokers with prostate cancer or to 99 with myocardial infarction.

Former smokers with prostate cancer had quit smoking an average of 23 years before their diagnosis; for myocardial infarction, the average interim was 10 years.

But smoking cessation was a more recent event for lung cancer patients, occurring, on average, just 2.7 years before diagnosis.

Further comparisons among former smokers revealed striking differences among the three groups.

"In the general population, you would expect that those who succeeded in quitting smoking would be those who smoked less and were less severely addicted, she said at the meeting sponsored by the International Association for the Study of Lung Cancer. "That is exactly what we found in patients with prostate cancer and myocardial infarction."

In contrast, current and former smokers with lung cancer had similar levels of cumulative tobacco exposure and identical median scores on a scale measuring severity of addiction—scoring 7 on a scale of 0 ("Didn't even think about it") to 10 ("The hardest thing I've ever done.")

Surprisingly, many of these lung cancer patients reported they had quit smoking with ease and with no symptomatic "alarm bell" that compelled them to stop.

Among the 55 patients who quit smoking before being diagnosed with lung cancer, 49 (89%) were reportedly asymptomatic at the time. Nearly a third (17 of 55) reported quitting "with no difficulty," (0 on a scale of 0-7), even though they were moderately to severely addicted to nicotine based on the Fagerström Test for Nicotine Dependence scale.

Many lung cancer patients reported they had quit smoking with ease and with no symptomatic 'alarm bell.'

DR. CAMPLING

"The way some of these patients stop smoking is really quite peculiar," said Dr. Campling. A typical patient was "someone who had smoked a pack of cigarettes a day for 50 years and wakes up one day and forgets to light a cigarette [and then] realizes they don't need it anymore."

Dr. Campling and her associates hope their findings will be followed up with a long-term, prospective study of smokers to identify unusual patterns of smoking cessation that may precede a diagnosis of lung cancer. In the meantime, she suggested that clinicians pay attention to any highly unusual pattern of smoking cessation in a long-term, heavy smoker, just as they would a sudden loss of appetite.

Dr. Carolyn Dresler, moderator of the session and an official discussant of the paper, questioned whether memory distortions and attribution errors may have influenced patients' recall of their smoking histories and difficulty quitting.

In addition, little is known about the ease of quitting experienced by the majority of smokers who stop smoking cold turkey, said Dr. Dresler, a cardiac and thoracic surgeon who heads the Arkansas Department of Health.

Dr. Campling and her associates reported no financial disclosures with respect to their study. ■

Dr. Philip Marcus, MPH, FCCP, comments: *Smoking cessation remains a goal of all physicians for their patients. What this study reports, if confirmed, could lead to the discovery of substances that promote or retard smoking. Some patients report that they can stop "cold turkey," and the ease of their stopping may cause one to wonder why it is so easy. Perhaps we should think further about current smokers who can stop easily, and repeat a chest x-ray just to be sure!*

Iloprost Cuts Endobronchial Dysplasia in Ex-Smokers

BY BETSY BATES
Elsevier Global Medical News

SAN FRANCISCO — Endobronchial dysplasia was significantly improved in former smokers who received oral iloprost, a synthetic form of prostacyclin, during a phase II, placebo-controlled chemoprevention trial presented at the World Conference on Lung Cancer.

"We saw improvement at all different stages of dysplasia. This holds for [grade] 2s and 3s" as well as higher-grade lesions, study investigator Dr. Robert Keith said at a press conference. "Based on these results, I think iloprost is a very promising agent … and a great candidate to move forward to a larger, phase III trial."

Biopsies obtained during baseline bronchoscopies revealed at least mild dysplasia in approximately 65% of 152 current and former smokers who were enrolled in the multicenter Iloprost Chemoprevention Trial directed by Dr. Keith, a pulmonologist at the University of Colorado, Denver.

Most study participants were male and white, and had smoked, on average, a pack of cigarettes a day for 50 years. Those classified as former smokers had to have stopped smoking for at least a year and were tested for nicotine exposure during the trial.

Following baseline bronchoscopies, 41 current smokers and 36 former smokers received placebo and 40 current smokers and 35 former smokers began an escalating oral dose of iloprost. The maximum dose was 150 mcg twice daily, Dr. Keith said at the meeting, sponsored by the International Association for the Study of Lung Cancer.

At 6-month follow-up, repeat biopsies were taken from each of six standardized sites and any other site biopsied at baseline.

Histologic improvement was seen in every former smoker who received iloprost.

In biopsies of former smokers, the composite histologic grade per patient declined from 2.12 to 1.73 according to World Health Organization classifications ranging from grade 1 (normal) to grade 8 (cancer). When the analysis included only subjects who had abnormal biopsies at baseline, the grade decreased from 3.27 to 2.06, and in their worst lesions, from 4.57 to 3.10.

Investigators also calculated a dysplasia index for each study participant, calculated as the number of biopsies with dysplasia (at least grade 4 on the WHO scale), divided by the total number of biopsies multiplied by 100.

The mean dysplasia index for former smokers went from 20.81 to 10.90 in all patients, and from 43.18 to 19.58 in the subgroup of former smokers who had abnormal biopsies at baseline. No significant changes were seen in histologic grades or dysplasia index scores in current smokers enrolled in the trial.

'We saw improvement [with iloprost] at all different stages of dysplasia. This holds for [grade] 2s and 3s.'

DR. KEITH

Side effects associated with vasodilator use were seen more frequently in patients receiving iloprost than in those taking placebo. Most prominent was headache, reported in 40 patients receiving iloprost and in 17 receiving placebo. Other less common side effects included flushing, nausea, pain, and myalgias. Serious adverse events were more common in the placebo group than in the iloprost arm.

The majority of lung cancer in the United States is diagnosed in former smokers, the group that benefitted from iloprost as a chemopreventive agent in the trial. To these patients, Dr. Keith said, "I can't change what you did, but maybe I can change what happens to you as we move forward."

In the United States, iloprost (marketed under the name Ventavis) is available only as an inhalation solution approved for the treatment of pulmonary arterial hypertension. At the time of the study, Schering AG manufactured iloprost and provided an oral form of the drug for the trial. Actelion Pharmaceuticals US Inc. now markets Ventavis in the United States.

The trial was funded through the National Cancer Institute, and neither Dr. Keith nor his associates reported any other relevant financial disclosures. ■

View a video interview of Dr. Keith at www.youtube.com/watch?v=0J_F-JwWnAg.

Dr. Philip Marcus, MPH, FCCP, comments: *For once, we have some possible good news about lung cancer. The investigators utilized an agent commonly used for the treatment of pulmonary hypertension and looked at lung cancer prevention in current and former smokers. Benefits were seen in former smokers, but not in current smokers. This study may serve as the basis to investigate many other compounds in a similar fashion. This is an area that has not been investigated before, and the results are promising.*

Shortage of Cardiothoracic Surgeons Predicted

Even under the most optimistic assumptions, the supply of cardiothoracic surgeons will fall.

BY ROBERT FINN
Elsevier Global Medical News

Within the next 10 years the demand for cardiothoracic surgeons will greatly exceed the supply, according to a study appearing in the journal Circulation.

If current trends continue, the demand for cardiothoracic surgeons could increase by 46% between 2005 and 2025. Over the same time period, the supply of such surgeons will decrease 21% as a result of retirement coupled with insufficient numbers of physicians entering the specialty (Circulation 2009 Aug. 11:doi: 10.1161/CIRCULATIONAHA.108.776278).

Patients are likely to suffer if non–board-certified physicians fill the gap left by cardiothoracic surgeons or if patients delay care because of the shortage, wrote Dr. Atul Grover of the Association of American Medical Colleges (AAMC, Washington) and coinvestigators. "Multiple strategies for ensuring adequate access to care must be explored if this crisis is to be averted."

'MULTIPLE STRATEGIES FOR ENSURING ADEQUATE ACCESS TO CARE MUST BE EXPLORED IF THIS CRISIS IS TO BE AVERTED.'

The investigators projected the supply and demand of cardiothoracic surgeons using a variety of assumptions. From the American Medical Association Masterfile for 2005, they identified 4,734 currently practicing cardiothoracic surgeons. Recent survey data from an AAMC study suggested that the average age of retirement for cardiothoracic surgeons is 61 years and that 60% of physicians fully retire from clinical practice by age 65.

At the same time the investigators assumed that 130 new trainees will enter the workforce each year. This is an optimistic assumption given that only 84 of 126 positions offered through the national match were filled in July 2007. The investigators also calculated supply based on two alternative assumptions: a gradual increase in newly trained cardiothoracic surgeons to 150 per year or a continued decline to 75 per year.

Even under the most optimistic assumptions, the supply of cardiothoracic surgeons will fall. If 150 physicians complete training annually, starting immediately, there would still be a 9% decline in the total number of active cardiothoracic surgeons in 2020 compared with 2005. If only 75 complete training annually there would be a 34% decrease in the number of cardiothoracic surgeons by 2020.

The investigators projected the demand under several alternative scenarios based on the increasing numbers of people over the age of 65 years, current patterns of health care use, and likely trends in technology. By 2020, the population of people over the age of 65 years will grow by 50%, and by 2030, there will be almost twice as many people in this age group as there were in 2005.

The most optimistic scenario assumes that coronary artery bypass grafting (CABG) will be completely eliminated over the next decade, decreasing the demand for cardiothoracic surgeons by about 40%. While the numbers of open revascularizations have been declining in recent years, few suggest that they will disappear completely.

Offsetting this decline in demand is an expected 20% increase in per capita rates of non-CABG cardiac and a general thoracic operations, including valve procedures, other open-heart procedures, and lobectomies or pneumonectomies. Taking all assumptions into account, the investigators calculated that there would be a shortage of 1,500 surgeons, equivalent to 25% of the projected need, by 2025.

The study was supported by the American Association for Thoracic Surgery and the Society of Thoracic Surgeons. The investigators disclosed no other conflicts of interest. ■

System Revises Cancer Stages

Lung Cancer • *from page 1*

dissatisfaction among oncologists around the world."

The 7th edition of the guidelines is available as a handbook, a manual, a CD-ROM, and posters for the clinic, and is aimed at medical oncologists, surgeons, radiation oncologists, and pathologists.

Highlights of the new staging system for non–small cell lung cancer (NSCLC) include the following:

► New subcategories of stage T1 (early-stage) disease are based on size: Tumors measuring 2 cm or smaller will now be classified as T1a, whereas tumors larger than 2 cm and up to 3 cm will be classified as T1b. T2 disease will also be subdivided into T2a (tumors larger than 3 cm and up to 5 cm) and T2b (tumors larger than 5 cm and up to 7 cm).

► A new category (T3) will be used to describe tumors larger than 7 cm.

► Patients previously considered T4 because of additional tumor nodules in the same lung as the primary tumor will now be classified as T3. If these patients are node negative, they will be considered to have stage IIB disease.

► Patients with additional tumor nodules in the bilateral lung (previously M1) will now receive a designation of T4, and they will be down-staged from stage IV to stage IIIA.

► The presence of malignant pleural effusions, long referred to by oncologists as "wet IIIBs" and treated as if the patient had disseminated disease, will now be officially staged that way, as stage IV disease.

► Specifically, pleural dissemination will no longer be classified T4, but will now fall into a new category (M1a), the same designation given when additional nodules are found in the contralateral lung.

► Distant metastases will be subclassified within M1 as M1b disease.

► Staging changes will include the reclassification of patients with T2b tumors (5-7 cm) who have node-negative disease to stage IIA.

► Patients with T3 tumors (larger than 7 cm) will be considered to have stage IIB disease if they are node negative, but stage IIIA if they have associated features of M1, listed above.

The "N" classification within TNM that describes the number of involved lymph nodes will remain unchanged in the 7th edition.

"We should recognize that this simple statement reflects an enormous step forward, because this is the first time that these 'N' descriptions we have been using for decades have actually been validated," said Dr. Goldstraw. The "N" subcommittee, after exhaustive review, concluded that the current system is accurate and required no revisions, he explained.

BY ANALYSIS OF LARGE DATABASES, THE NEW SYSTEM IS EXPECTED TO ASSESS AN INDIVIDUAL PATIENT'S PROGNOSIS MORE ACCURATELY.

The new system will also resolve disagreements between Japanese and American systems of categorizing regional lymph node involvement, a dispute that divided the lung cancer world. Now, there will be a singular method of nodal involvement patterns within well-characterized zones, he said.

Through analysis of survival in large databases based on tumor size and disease proliferation, the new staging system is expected to assess an individual patient's prognosis more accurately. It promises to considerably alter the discussion between clinicians and patients about the potential advantages of surgery, radiation, and/or chemotherapy, as well as to better categorize patients enrolled in clinical trials.

For example, patients who are down-staged because additional tumors are found in the same lobe as the primary tumor may now be considered candidates for adjunctive chemotherapy along with surgery. Similarly, there may be a greater role for surgery in patients with metastatic nodules in the bilateral lobe who previously would have been assigned a stage IV diagnosis, but are now stage IIIA.

The multidisciplinary nature of the new system is evident in the specificity of pathological and radiologic parameters used to characterize each stage of disease.

"Pathologists asked us to look at the issue of visceral pleural invasion," said Dr. Goldstraw. In the past, this has been

difficult to define and categorize, he explained; as a result, a uniform definition has now been agreed upon for the first time.

Medical oncologists will find a host of prognostic variables in the new guidelines, including performance status, age, sex, laboratory values, initial maximum standard uptake variable on initial PET scan, and a review of meta-analyses of the current stage of knowledge about the prognostic significance of biological markers.

In addition to changes in the staging of NSCLC, analysis of more than 13,000 cases of small cell lung cancer—the largest such database in the world—reaffirmed the usefulness of the TNM system in that disease.

Previously, staging guidelines for SCLC were primarily used by surgeons, whereas medical oncologists have tended to simply dichotomize patients as having extensive or limited disease, explained Dr. Goldstraw during the press conference.

Upcoming steps in efforts to modernize lung cancer staging will include the correction of geographical and treatment biases within retrospective data, the inclusion of prospective data based on the new staging system, implementation of a Web-based system for world data collection, and the extension of staging updates to include neuroendocrine tumors and mesothelioma.

Dr. Elisabeth Brambilla, chair of the IASLC pathology committee and chair of pathology at University Medical Center Grenoble (France), discussed the idea of dividing early-stage tumors according to a more finely defined measurement of solid invasive components, as opposed to the ground-glass opacity that can sometimes be visualized on CT scans. When multiple nodules are present, future staging parameters may be able to incorporate molecular features, so that primary vs. metastatic tumors can be determined, she said.

Dr. Edward F. Patz Jr., professor of radiology, pharmacology, and cancer biology at Duke University in Durham, N.C., said the new size criteria within the guidelines will require precise specificity by radiologists.

"We need to be enormously careful about this," he said, cautioning that an overenthusiastic reading of tiny, likely benign nodules could serve to up-stage a patient, with significant treatment implications. "You can't write the patient off, because we do see small nodules," he said.

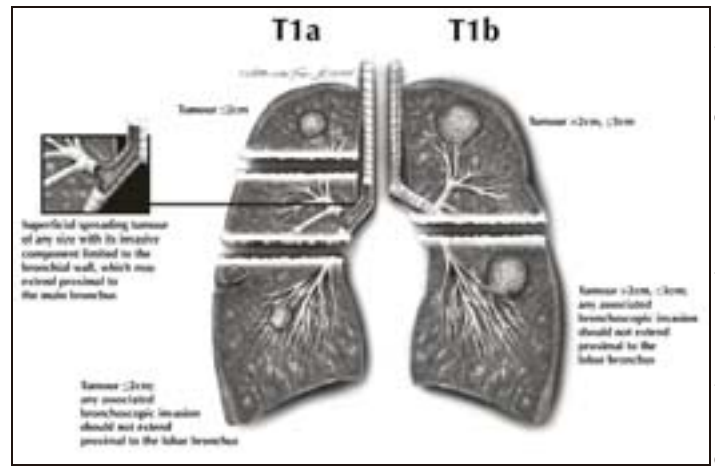
Dr. Patz recalled a mentor once telling him, "A radiologist with a ruler is a radiologist in trouble." He urged colleagues to be circumspect in writing their reports, and simply characterize what they see rather than make inferences about the malignant potential of the small lesions on a scan.

He also warned that current imaging modalities are not uniformly accurate when it comes to lymph nodes and nodal groups.

CT scans are about 60% sensitive and specific in identifying involved nodes, whereas PET scans increase the accuracy to about 80%. ■

To view a video interview of Dr. Goldstraw, go to www.youtube.com/watch?v=2AjtjGuAUwk.

Dr. W. Michael Alberts, FCCP, comments: *I am sure that we will all be carrying around another pocket card (or find a new PDA application) until the new system becomes more familiar. It is impressive, however, that the new lung cancer staging system was derived from data compiled from more than 100,000 lung cancer cases from 46 centers in 19 countries.*



Courtesy International Association for the Study of Lung Cancer (IASLC). Copyright 2008 Aletta Ann Frazier, MD.

New subcategories of stage T1 disease based on tumor size have been created in an effort to more accurately assess an individual patient's prognosis.

Full Adoption Reduced Infections

Compliance • *from page 1*

specific infection control problems that are most pressing in their institutions, she said.

As part of a larger study, the survey was sent to infection control specialists responsible for process and outcome surveillance. Participants were asked about their ICU policies with regard to central line bloodstream infections (CLBSIs) and ventilator-associated pneumonia (VAP), CLBSI and VAP infection rates, and bundle compliance rates.

The CLBSI bundle consisted of barrier precautions, use of chlorhexidine, optimal site selection, and daily site checks for signs of infection. The VAP bundle consisted of periodically raising the patient's head and periodically interrupting sedation to facilitate deeper breathing.

In all, 250 hospitals (57%) responded. Respondents provided data on 415 ICUs, including 223 (54%) medical/surgical units. A total of 284 ICUs (68%) had adopted the full VAP bundle, and 204 (49%) had adopted the full CLBSI bundle. The mean infection rates per 1,000 device-days were 2.6 for VAP and 2.1 for CLBSI.

Rates of device-associated infections were significantly lower only in the ICUs that correctly implemented all bundle components at least 95% of the time (73 ICUs for VAP and 35 ICUs for CLBSI).

Some believe that the ability to keep infection rates low stems from the overall quality of care in an ICU, but this study attributes low infection rates to highly targeted efforts aimed at specific infections in which the unit focuses on all components of a bundle at least 95% of the time, said Dr. Stone, who is also an RN, in an interview. No single component of either bundle significantly reduced infection rates.

"Moreover, always implementing the ventilator bundle correctly was not significantly associated with decreased CLBSI, and vice versa," she said.

"If you're just focusing on one problem, you don't get to be a better ICU."

Dr. Stone received support for this study from the National Institute of Nursing Research. ■

Study Identifies Risk Factors for Infection-Related ARDS

BY DOUG BRUNK
Elsevier Global Medical News

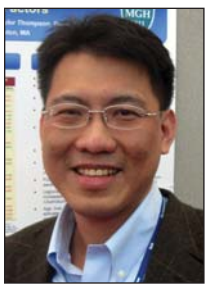
SAN DIEGO — Infection-related acute respiratory distress syndrome has a higher mortality rate than non–infection-related acute respiratory distress syndrome, and is influenced by specific clinical factors, infection sites, and pathogens, according to results from a large study.

To learn more about infection-related ARDS and to explore the factors associated with the development and survival of this syndrome, investigators led by Dr. Chau-Chyun Sheu conducted a prospective observational study of 2,250 critically ill patients with clinical risk factors for ARDS.

The patients were enrolled upon admission to the intensive care unit at Massachusetts General Hospital and Beth Israel Deaconess Medical Center, Boston.

Patients with infection-related ARDS presented with bacteremia, sepsis, or pneumonia on admission and later developed ARDS, the researchers wrote in a poster presented during an international conference of the American Thoracic Society. Patients with non–infection-related ARDS presented with trauma, multiple transfusions, or aspiration without bacteremia, pneumonia, or sepsis on admission, and developed ARDS later. The investigators followed up all the ARDS cases for all-cause 60-day mortality.

The researchers reported that most of the ARDS cases (90%) were infection related, and occurred in 626 of the 2,118 patients who were admitted to intensive care units with sepsis, pneumonia, or bacteremia. In addition, infection-related ARDS patients had a significantly higher 60-day mortality rate, compared with their counterparts who had non–infection-related ARDS (38% vs. 27%, respectively). A total of 62% of ARDS patients were male, with a mean age of 69 years, while 62% of the non–infection-related ARDS patients also were male, but were somewhat younger, with a mean age of 63 years. A total of 90% of those with ARDS were white, as were 92% of those with the non–infection-related ARDS.



The 60-day mortality rate was 38% in infection-related ARDS and 27% in non–infection-related ARDS.

DR. SHEU

When the investigators performed a multivariate analysis, they found that the following factors were associated with an increased risk of infection-related ARDS development: septic shock (odds ratio 2.3), multiple infection sites (OR 1.3), pulmonary infection (OR 3.8), abdominal infection (OR 1.7), and fungal infection (OR 2.1). Surprisingly, bacteremia and septic shock were not associated with mortality in infection-related ARDS, nor was any individual infection site.

Infections with *Legionella* (OR 5.5) and *Bacteroides* (OR 3.1) were associated with increased risk of developing infection-related ARDS, while methicillin-resistant *Staphylococcus aureus* (OR 0.6) and *Clostridium difficile* (OR 0.1) were associated with a decreased risk.

Infections with coagulase-negative *Staphylococcus* (HR 2.2) and *Pseudomonas aeruginosa* (HR 1.9) were associated with increased infection-related ARDS mortality.

Other factors associated with increased infection-related ARDS mortality were advanced age, liver cirrhosis, history of steroid use, and higher serum creatinine and serum bilirubin levels, while treatment with activated protein C was associated with decreased mortality.

In an interview, Dr. Sheu acknowledged that there were certain limitations to the study, including the inability to assess causality as opposed to association.

"Also, we didn't collect the data on antibiotic appropriateness and time to meeting resuscitation goals," said Dr. Sheu of the Harvard School of Public Health's department of environmental health in Boston. "These were potentially confounding factors in our study."

The study was supported by a grant from the National Institutes of Health. ■

CHEST 2009 Will Usher in a New ACCP President

During Convocation ceremonies at CHEST 2009 next month, Dr. Kalpalatha K. Guntupalli, FCCP, will be inaugurated as the new ACCP President. She is a Professor and Chief, Pulmonary/Critical Care and Sleep Section, at the Baylor College of Medicine in Houston, TX. Dr. Guntupalli has served ACCP in many capacities, including Regent-at-Large; Chair of the Critical Care Institute; Chair of Women's Health NetWork; member of the CHEST Program Committee; and trustee of The CHEST Foundation. She currently serves as The CHEST Foundation's Second Distinguished Scholar in Critical Care Medicine.

Her academic interests include ARDS and critical care education tools. She has developed antitobacco education material in seven languages and antitobacco

'I want to realize the concept of the "global family" by increasing our reach to the international community.'

DR. GUNTUPALLI

cartoons for children in three languages, inspiring more than 200,000 children. Dr. Guntupalli is the recipient of numerous awards, including the "Parker J. Palmer Courage To Teach" award from the ACGME, and "Master of American College of Physicians" (MACP) award from the ACP. Dr. Guntupalli believes in fostering a culture of a "global family" of health caregivers to deliver the best of care to all patients and make meaningful contributions to society.

We asked Dr. Guntupalli to share some thoughts on her upcoming presidential term.

Q. What would you like to accomplish as President of the ACCP?
As the President of the ACCP, I will strive to retain and further strengthen the role of ACCP as the premier organization representing professionals who promote cardiopulmonary health throughout the world.

I want to actualize/realize the concept of the "global family" by increasing our reach to the international community. As an international medical graduate myself, I am aware of the value of the excellent education programs and the tools for public outreach delivered by the ACCP. Through meaningful engagement of the leaders, members, and sister organizations around the globe, we can be a global family. I believe that by fostering the active interchange of ideas and activities and the engagement of domestic and international members, sister organizations, and other partners, we will remain the world leader.

The year 2010 has been declared as the Year of the Lung by the Forum of International Respiratory Societies; the ACCP will participate and contribute to celebrate lung health worldwide. On the domestic front, I would like to make ACCP the "one stop shop" for the education, practice management, performance improvement/monitoring, and advocacy needs of the membership.

Q. What do you consider to be the greatest strengths of the ACCP and how will you build upon them?
ACCP has always been a "member-friendly" and "member-responsive" organization that promotes continuing education and develops tools for improved practice management and patient care. With large US and international membership, ACCP is a champion for the voice of health-care professionals and patients with cardiopulmonary illnesses.

Q. What is the greatest challenge facing the College and how will you address it?
The current financial atmosphere and health-care debate are potential causes for concern to our members, sponsors, and partners that support the organization. We need to leverage our current strengths to explore new opportunities to continue to serve our members. I am very confident we will not only survive but thrive by forging new programs and partnerships.

Q. What is your charge to the members and new Fellows of the ACCP?
Members and new Fellows should remain actively engaged in the ACCP. Together, we can contribute and shape the change we want to accomplish in this era of health-care reform. ■

The CHEST Foundation Honors Al and Norine Lever

The CHEST Foundation is proud to recognize Alvin Lever, MA, FCCP(Hon) and his wife, Norine Lever, for their outstanding leadership of the ACCP and The CHEST Foundation. The Al and Norine Lever Honorary Endowment Fund was established to continue the Lever's practice of mentoring others by developing leaders in the field and strategic leadership initiatives that will transform pulmonary, critical care, and sleep medicine. By funding new generations of ACCP leaders who have demonstrated abilities in leadership, research, and innovation, the ACCP will continue to be a leading resource for clinical research and education and an avid proponent of patient-focused care.

During Al Lever's 18-year tenure, the ACCP has experienced unprecedented growth in all areas, including increases in membership, annual meeting attendance, and gross revenues that have nearly tripled since 1991. Norine Lever's accomplishments have been more family-oriented as she championed for the ACCP staff, members, patients, and their families. In 2001, Mrs. Lever proposed the creation of the Ambassadors Group, an auxiliary group for The CHEST Foundation. Ambassadors Group members have made it their charge to foster initiatives that augment The CHEST Foundation's programming in many areas.

To make your tax-deductible contribution to the Al and Norine Lever Honorary Endowment Fund, visit The CHEST Foundation's Web site at www.chestfoundation.org and make a secure online donation, or download an endowment brochure to use when mailing in your donation. For more information about donating to the fund, contact Teri Ruiz at truiz@chestnet.org or at (847) 498-8308. ■

ADCIRCA™ (tadalafil) Tablets

BRIEF SUMMARY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

CONTRAINDICATIONS

Concomitant Organic Nitrates

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

Hypersensitivity Reactions

ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIRCA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention.

PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIRCA is administered, the possibility of associated PVOD should be considered.

There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

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- M^qfbkqp t fqe obpqof`qfsb lo `lkdbpqfsb `^oafl j vlm^qev
- M^qfbkqp t fqe pfdkf«`^kq ibcq sbkqof`ri^o avpcrk`qflk
- M^qfbkqp t fqe ifcb*qeob^qbkfkd ^ooevqe j f^p
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Use with Alpha Blockers and Antihypertensives

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.

Use with Alcohol

Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.

Use with Potent CYP3A Inhibitors or Inducers

Co-administration of ADCIRCA in Patients on Ritonavir

In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Co-administration of Ritonavir in Patients on ADCIRCA

Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADCIRCA.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.

Use in Renal Impairment

In patients with mild or moderate renal impairment

Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.

In patients with severe renal impairment

Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Use in Hepatic Impairment

In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B)

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

In patients with severe hepatic cirrhosis (Child-Pugh Class C)

Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA.

Effects on the Eye

Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Hearing Impairment

Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Combination with Other PDE5 Inhibitors

Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

Effects on Bleeding

PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS

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

- Evmlqbkpflk
- Sfpflk ilpp
- Eb^ofkd ilpp
- Mof^mfp j

Clinical Trials Experience

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

Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients.

In the placebo-controlled study, the most common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥ 9% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

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

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

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

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

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.

Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis

Nervous — Migraine, seizure and seizure recurrence, and transient global amnesia

Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion

Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Urogenital — Priapism.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with ADCIRCA

Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life–threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

Alpha-Blockers

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.

Antihypertensives

PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood–pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.

Alcohol

Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Potential for Other Drugs to Affect ADCIRCA

Ritonavir

Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.

Potential for ADCIRCA to Affect Other Drugs

Cytochrome P450 Substrates

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).

Aspirin

Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.

P-glycoprotein *(e.g., digoxin)*

Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

Non–teratogenic effects

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

Nursing Mothers

It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ADCIRCA in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

Renal Impairment

For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.

In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Hepatic Impairment

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

OVERDOSAGE

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

Marketed by United Therapeutics Corporation, Research Triangle Park, NC 27709

Rx only June 2009

www.adcirca.com

Pulmonary Perspectives

Breath Biomarkers of Lung Cancer

Biomarkers may eventually help us identify individuals at risk of developing lung cancer, help to screen for lung cancer, diagnose the nature of a lung nodule, prognosticate the outcome of the cancer, or predict the tumors' response to therapy. A variety of avenues are being pursued in the search for biomarkers of lung cancer. Most of these involve the study of the molecular makeup of lung cancer tissue or blood. An alternative, readily available source of biomarkers is a person's breath.

Exhaled breath contains nitrogen, oxygen, carbon dioxide, water, and inert gases. In addition, volatile organic compounds (VOCs), generated in the body or absorbed from the environment, can be detected in the breath in very low concentration (parts per billion volume to parts per trillion volume). The exogenous molecules are inhaled into and absorbed through the lungs or absorbed through the skin. The endogenous molecules are generated by the biochemical processes of the body. Thus, measuring VOCs in the breath provides a window into the biochemical processes of the body. There is evidence that many biochemical processes are different in lung cancer cells than they are in normal cells. These differences are likely to lead to the production of different patterns of VOCs in the breath of people with lung cancer. If these differences are unique, consistent, and detectable, they could serve as useful biomarkers for lung cancer (Table 1).

Lab-based studies support this concept. Reports include comparisons of the head space gases of lung cancer cell lines, lung cancer cell culture media, naïve media, and non-cancer cell lines. These studies have identified different patterns of VOCs between the samples that were included.

Others have reported comparisons of breath VOCs from patients with lung cancer to those of subjects without cancer. Until recently, most studies have used gas chromatography and mass spectrometry (GC-MS) to identify a discriminatory set of VOCs in the breath of patients with lung cancer. With GC-MS analysis, the breath sample is usually preconcentrated onto a medium that is transported to the device where the VOCs are desorbed from the medium in order to be analyzed. GC-MS techniques allow specific VOCs to be identified and quantified. They can be sensitive into the low parts per billion or upper parts per trillion range with preconcentration. The disadvantages of GC-MS analysis are that some VOCs may be missed or lost in the concentration and desorption process; it takes a considerable amount of time to process and analyze a sample; the equipment is large and expensive; and it takes an experienced person to run it. GC-MS analysis of exhaled breath to help identify lung cancer has been reported (Mazzone. *J Thorac Oncol* 2008;3:774; Mazzone. *J Breath Res* 2008;3:10.1088/1752). A discriminatory group of volatiles has been identified. The accuracy of the models of discriminatory volatiles produced has ranged from 70% to 85%. These studies have differed in the number of subjects included, the stages of lung cancer, the manner in which the breath was collected, the type of control subjects included (*ie*, healthy vs disease), the pattern recognition statistical techniques used, and the means of validating the models that were developed.

More recently, advances in detecting technologies have been used to look at breath specimens. The devices being used have one major advantage over GC-MS. They are more sensitive, thus they do not require preconcentration of the breath sample. This leads to faster sample analysis (in some cases, near real time). They are also somewhat easier to use. The major disadvantage of many of these devices is that they are not able to fully identify the VOCs they are detecting (they identify a mass-charge ratio only) and may not be able to specify the concentration of the volatiles that are detected. Devices that have been reported include single ion flow tube mass spectrometry, ion mobility spectrometry, and proton transfer reaction mass spectrometry. These have been relatively small studies, showing promise for future development.

An alternative approach to the discovery of breath biomarkers has been analysis by nonspecific chemical sensor matrices. Many types of sensors exist, including conductive polymers, nonconductive polymer/carbon black composites, metal oxide semiconductors, fluorescent dye/polymer systems, quartz microbalance sensors coated with metalloporphyrins, polymer-coated surface acoustic wave devices, and chemoresponsive dyes. The principle of these sensor systems is that their output is altered when VOCs bind to them. The output might be a change in conductance, vibration, or color, depending on the type of sensor that is used. Some sensors are reusable, and others are disposable. They can be inexpensive, portable, and easy to use, making them ideal as a point-of-care test. Typically, their output is related to the mixture of VOCs they are exposed to, and, thus, they do not identify the specific compounds or concentrations present. They produce a "breathprint." The disadvantages of these systems are that they do not identify the specific compounds, and their limit of detection may not be quite low enough to sense all of the discriminatory volatiles. A few of these sensor matrices have been used in studies in patients with lung cancer. They have reported accuracies similar to those from GC-MS ((Mazzone. *J Thorac Oncol* 2008;3:774; Mazzone. *J Breath Res* 2008;3:10.1088/1752; Machado et al. *Am J Respir Crit Care Med* 2005;171:1286; Mazzone et al. *Thorax* 2007;62:565). As with GC-MS, the studies have differed in the number of subjects, stage of cancers included, type of control subjects, breath collection methods, statistical techniques used, and method of validation of their results.

There is still a lot of progress to make before breath VOC biomarkers have the chance to be clinically useful. Despite reports of reasonably accurate discrimination between cancers and controls, the models of VOC biomarkers have not been consistent between studies. Many studies have not included the spectrum of lung cancer patients seen clinically or looked for differences in breath VOCs related to these differences (*eg*, histologic findings, stage, outcome). Many studies have not included a group of control subjects similar to those in whom the biomarker would be used as a clinical test. The ideal method of breath collection (an alveolar breath sample or a mixed sample), and the need to control for ambient volatiles to maximize the accuracy of the breath biomarker, have not been determined. Insight into the origin of the discriminatory VOCs is largely lacking. This may be necessary for widespread acceptance and clinical application. Advances in sensing technologies will need to be translated into reliable, easy to use, inexpensive, point-of-care tests. As progress is made in each of these areas, other applications of breath VOC biomarker development can be explored. It is possible that breath biomarkers will be able to provide information about the prognosis of the cancer or help predict the response of the cancer to different therapies.

Today, many groups around the world are working hard to discover clinically useful biomarkers, certain to benefit our patients with lung cancer. Groups invested in discovering breath VOC biomarkers have an unusual source of inspiration. A study that assessed the ability of dogs to distinguish the breath of subjects with lung cancer from healthy control subjects reported that the dogs were 99% accurate (McCulloch et al. *Integr Cancer Ther* 2006; 5:30). As our understanding and technology improve, we may approach this level, with the potential to impact many levels of lung cancer management. ■

Dr. Peter Mazzone, FCCP
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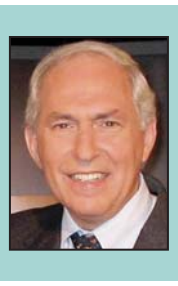
Table 1. ***VOCs Present in Greater Concentration in Breath of Patients With Lung Cancer***

- Acetone
- Acetophenone
- 1,2,4-Trimethylbenzene
- Benzene
- Decane
- 2,2,4,6,6-Pentamethylheptane
- 2,4-Dimethylheptane
- Heptane
- Hexene (1-)
- Isoprene
- Octane
- 2-Methylpentane
- Pentane
- Styrene



Dr. Gene L. Colice, FCCP
Editor,
Pulmonary Perspectives

Editor's Insight

Dr. Mazzone describes the earliest steps in an extremely fascinating area, the analysis of exhaled breath as a reflection of metabolic activity in the lungs. We have already seen how exhaled nitric oxide levels may help in the management of asthma, and now we learn more about the possible use of exhaled breath volatile organic compounds for identifying lung cancer.

This observation comes at an extremely important time. Lung cancer is already a huge public health problem, but, as the number of smokers both in the United States and around the world increases, lung cancer will become even more of a concern in the near future. Pulmonary physicians recognize the difficulty in identifying lung cancer early enough to enable curative surgical resection.

Huge trials are ongoing in the United States and Europe, evaluating CT scans as a possible screening tool for detecting lung cancer. Whether these studies successfully demonstrate the value of chest CT scans as an early detection tool for lung cancer or not, it seems entirely reasonable to wonder whether combining analysis of exhaled breath volatile organic compounds with chest CT scans might improve our ability to identify early lung cancer.

SLEEP STRATEGIES

Complex Sleep Apnea Syndrome

There are few topics in the field of sleep medicine as controversial as complex sleep apnea syndrome (CompSAS). Recent debates as to its existence have been featured at national meetings and in the literature (Gay. *J Clin Sleep Med* 2008; 4:403; Malhotra et al. *J Clin Sleep Med* 2008; 4:406).

Much of the dispute about the disease has focused on the liberal use of the term to encompass other problems that patients may have after continuous positive airway pressure (CPAP) titration. Strictly speaking, CompSAS is defined as the appearance of central sleep apnea after treatment of a patient with obstructive sleep apnea (OSA) who has had CPAP therapy. A more elegant definition, based on the pathophysiology of concomitant upper airway obstruction and respiratory control dysfunction, was recently proposed (Thomas et al. *Sleep* 2007; 12:1756). Some studies (Yaegashi et al. *Intern Med* 2209; 48:427; Morgenthaler et al. *Sleep* 2006; 29:1203) have retrospectively examined records of patients with OSA treated with CPAP to assess the prevalence of the disease using these definitions, with estimates ranging from 5.7 to 15%.

When initially reported in 1991, complex sleep apnea was thought to be secondary to the initial exposure to CPAP. The explanation proposed was that patients would arouse frequently due to discomfort from the device; the frequent central apneas noted were simply the normal decrease in respiratory drive during the transition from wakefulness back to sleep (Marrone et al. *Eur Respir J* 1991; 4:660). Labeling the events as side effects of therapy makes sense because the majority of patients do not demonstrate significant central sleep apnea during diagnostic polysomnography. Other explanations of disease development have arisen, also relating the central events to the administration of CPAP. One such explanation proposes that the improvement in airways resistance and dead space seen after treatment of OSA with CPAP improves the effectiveness of the ventilatory pump; the improved carbon dioxide clearance leads to a decrease in arterial CO_2 to levels below the apneic threshold, inducing central events. A simpler mechanism attributes complex sleep apnea to the activation of stretch receptors, leading to ventilatory inhibition.

More recent investigations have demonstrated certain features of affected patients that may predispose them to the development of CompSAS. Several studies have shown that affected patients are more likely to be men and tend to have a lower BMI than patients with OSA, though these data have not been replicated consistently. Comparisons of diagnostic findings on polysomnography in patients diagnosed with CompSAS tend to show more frequent events during nonrapid eye movement sleep compared with their counterparts who have OSA. This suggests a possible component of central sleep apnea even prior to CPAP therapy because central events typically attenuate during rapid eye movement sleep. The presence of an underlying tendency towards centrally mediated disease was supported by a retrospective analysis of patients with and without CompSAS using ECG-based spectral analysis (Thomas et al. *Sleep* 2007; 30:1756), showing a 95.2% sensitivity and 85.7% specificity for predicting the development of predominantly central sleep apnea after CPAP implementation. Whether this tool can be used to prospectively identify individuals who are at risk for CompSAS remains to be seen, in part, due to the difficulty in measuring the relevant variables in clinical sleep laboratories.

Another question about CompSAS relates to its clinical relevance. If the disease does not impact clinical outcomes, does it matter? A case series from the Mayo Clinic (Pusalavidyasagar et al. *Sleep Med* 2006; 7:474) showed that 87.9% of patients with the disease were treated with CPAP despite the persistence of central events during CPAP titration. Although more complaints about CPAP removal were noted among patients with CompSAS during follow-up visits, there was no difference in CPAP compliance or change in Epworth sleepiness scale score between CompSAS patients and those with OSA. Based on available data, there is a strong suggestion that CompSAS will improve over time, although some of studies have been faulted for a significant loss to follow-up, and no long-term evaluations of other clinical endpoints, such as cardiovascular morbidity, exist. Nevertheless, the resolution of events in the majority of patients is certainly consistent with the similar symptomatic benefit seen with CPAP in patients with CompSAS and OSA. Given these facts, it may be reasonable to treat these patients in the same fashion as those with OSA and reassess some time later, although even this recommendation is not evidence-based.

Traditional approaches to treating central sleep apnea have also been used in complex disease. Medical optimization of the factors that might exacerbate central apnea, such as congestive heart failure or the use of narcotics, is recommended. Case reports supporting the use of acetazolamide for central apnea have also been published. Some have extrapolated these data to advocate for acetazolamide use in patients with complex disease, based upon its induction of metabolic acidosis and inhibition of peripheral chemoreceptor response to changes in carbon dioxide; however, the data are far less robust. The use of theophylline could also be considered, although the potential adverse effects make it significantly less attractive.

As the understanding of the mechanisms underlying complex sleep apnea have evolved, therapies specifically targeted at the suspected pathophysiology have arisen. Routine use of standard bilevel positive airway pressure devices in patients with CompSAS is relatively contraindicated, as it is thought to worsen the disease by overventilating the patient, causing the arterial CO_2 level to drop below the apnea threshold. CPAP devices with variable ventilatory support have subsequently been developed and can be used to target a specific minute ventilation; some of these have shown benefit in subgroups of patients who had previously failed CPAP titration (Allam et al. *Chest* 2007; 132:1839), but no long-term randomized trials comparing the novel devices with standard CPAP among patients with CompSAS have been published.

Methods of maintaining the arterial CO_2 tension at levels above the apnea threshold should also be effective in treating complex sleep apnea. There are no clinical trials of such interventions in complex disease, but published case reports demonstrate the efficacy of enhancing dead space volume and increasing inspired CO_2 concentrations. Concern about the safety of such interventions outside of monitored settings may limit their clinical utility until further data beco me available. Some have advocated for using slightly subtherapeutic levels of CPAP to allow for some mild flow limitation to persist, arguing that this will prevent the hypocapnia seen with

Continued on following page

Dr. James Parish, FCCP
Section Editor,
Sleep Strategies

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If you only think of lectures and exhibits when you think about an annual medical meeting, it's time to think again and "Experience CHEST 2009."

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CHEST 2009 online registration is open through October 29, and on-site registration begins October 30. Learn more and register at www.chestnet.org. Watch for special celebrations and events at CHEST 2009, as the ACCP celebrates 75 years of inspiring leadership, education, communication, and clinical practice. ■

CHEST 2009

October 31 - November 5
San Diego, California

Continued from previous page

complete alleviation of obstructive apnea (Gilmartin et al. *Curr Opin Pulm Med* 2005; 11:485).

What should a provider do with a patient found to have CompSAS during a CPAP titration? Based upon available data, it is not clear that anything specific need be done; implementation of CPAP seems reasonable given the frequency with which the phenomenon is self-limited. Follow-up reassessment of disease using polysomnography may be appropriate, particularly if the patient continues to complain of difficulty with device tolerance after normal troubleshooting maneuvers have failed. The use of a variable pressure-support device may be effective, but concomitant interventions to minimize the severity of centrally mediated events, such as optimization of heart failure, if present, should also be undertaken. Until additional data regarding long-term outcomes of complex sleep apnea become available, the best treatment may well be the one that leaves the patient feeling refreshed in the morning. ■

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Chief, Pulmonary/Critical Care Medicine
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Attend 11th Annual Making a Difference Awards Dinner

Saturday, October 31, 2009
Manchester Grand Hyatt San Diego
Open Reception: 7:00 PM to 7:45 PM
Dinner and Ceremonies: 8:00 PM to 10:30 PM

This year's dinner will kick off the ACCP's 75th anniversary celebration. There will be a 75th anniversary display at the venue that correlates with an interactive trivia game that will be played by everyone attending the dinner. So, make sure you take the opportunity to look the display over during the reception.

This is the 11th year that The Foundation will confer the newly named D. Robert McCaffree, MD, Master FCCP Humanitarian Awards to deserving projects supported by ACCP members' expertise and volunteer time. This year, $50,000 will be awarded to six winning projects, including one Ambassadors Group Humanitarian Recognition Award. Each of these projects exemplify best practices of care and serve families worldwide who otherwise would be unable to access or afford medical care.

Another exciting part of the celebration that evening will be the announcement of the Al and Norine Lever Honorary Endowment Fund. This endowment will continue the Lever's practice of mentoring others by developing leaders in the field and strategic leadership initiatives that will transform pulmonary, critical care, and sleep medicine.

The ACCP Industry Advisory Council will also present their annual monetary award to the Community Outreach Event partner, Santee School District Foundation, which will benefit Sycamore Canyon Elementary School.

Dinner invitations will be mailed after Labor Day. We hope that you will be able to join your colleagues and friends for an evening of celebration and fun. Ticket price is $150 per person ($25 of ticket price is tax-deductible), and online registration is available for those purchasing a ticket at www.chestfoundation.org. Making a Difference Society members at the $1,000 level are eligible for two complimentary tickets, and annual donors at the $500 level are eligible for one complimentary ticket, upon request. Contact Teri Ruiz at truiz@chestnet.org or (847) 498-8308 to obtain more information.

The CHEST Foundation's 11th Annual Making a Difference Awards Dinner sponsors, to date, are: AstraZeneca, LP; Boehringer Ingelheim Pharmaceuticals, Inc.; Holland & Knight, LLP; Merck & Co., Inc.; Nycomed, Inc.; Pfizer, Inc; and sanofi-aventis. ■

Donate Your Honoraria to The CHEST Foundation

ACCP members and CHEST faculty have been generously donating their honoraria to The CHEST Foundation for many years. This method of contributing has proven to be an easy way for donors to give to The Foundation while they enjoy the professional interaction with their peers at ACCP educational programs and pharmaceutical focus groups. Those contributing their honorarium to The CHEST Foundation are supporting The Foundation's four areas of focus: tobacco prevention, clinical research, humanitarian service, and critical care/end-of-life care.

This fall, ACCP members can direct their honorarium to a new campaign developed by Dr. Jay I. Peters, FCCP – Physicians Speaking for Humanity or PS4H. PS4H is an appeal to physicians who lecture and/or attend pharmaceutical focus groups to donate their honorariums to The CHEST Foundation to support the pro bono service of ACCP members through The Foundation's Humanitarian Service Program.

Prior to CHEST 2009, CHEST faculty members can indicate online that all or a portion of their honorarium should be made payable to The CHEST Foundation. The designated amount will automatically be given to The Foundation as a charitable contribution in their name, and any remainder due will processed and mailed by the ACCP.

This donation clearly benefits The Foundation and may be a benefit to you by reducing your annual income at year-end. Canadian members donating in this way are allowed to donate US income and claim the eligible amount of the gift allowed on a US tax return, up to 75% of the net US income on a Canadian tax return.

If you are interested in donating honoraria received as faculty at CHEST 2009 or at outside pharmaceutical engagements to The CHEST Foundation's annual fund or the PS4H campaign, contact Teri Ruiz at truiz@chestnet.org or (847) 498-8308. ■

EDUCATION INSIGHTS

AQuIRE Knowledge and Performance Tool Debuts

BY JOYCE BRUNO REITZNER, MBA, MIPH
Assistant Vice President, Quality Improvement

A number of medical specialty society-driven patient registries and databases exists. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) registry has been successful in establishing practice benchmarks among participating hospitals. The American College of Cardiology National Cardiovascular Data Registry (NCDR) has established nationally recognized indicators to measure quality care, and The Society of Thoracic Surgeons National Database realized a milestone when The Society was successful in attaining higher reimbursement rates for certain procedures.

The American College of Chest Physicians (ACCP) now offers the ACCP Quality Improvement Registry, Evaluation, and Education (AQuIRE) to assist the chest physician to meet increasing demands placed upon them by the public, credentialing bodies, regulatory agencies, payers, and the institutions in which they practice.

AQuIRE combines data collection, quality and data reporting, and pathways to targeted education to increase knowledge and performance in deficient areas. Participation provides participants with the ability to enhance their practice through the application of useful data reports and peer comparisons. Pulmonary, critical care, and sleep physicians will now have a tool to more easily monitor their practice, understand of how they trend among their peers, and provide direction in the development of indications, which will someday be used to determine reimbursement.

Currently, two registries are available for participation—the Bronchoscopy Diagnostic Registry and the Bronchoscopy Interventional Registry. The overall purpose of these registries is to assist with establishing national standards for competency and to understand treatment patterns, clinical outcomes, device safety, and the overall quality of care for patients undergoing bronchoscopy.

Beginning February 20, 2009, pilot testing for the AQuIRE Bronchoscopy Module was initiated. To date, there are 10 academic, community-based, and private practice centers participating. As of August 2009, 750 procedures have been entered.

Bronchoscopy Module Features

- No cost, Web-based data collection and download tools
- Real-time reporting on quality indicators
- Ability to access your current data at anytime
- Comparative institutional outcomes reports to enable benchmarking with peers and the national experience
- Access to clinically and technically experienced support
- Participant training resources

How Can I Use These Data Reports?

- Optimize resource consumption to reach the maximum quality of care.
- Examine the impact of practice changes and new technologies on patient care and consumption.
- Monitor your indicators and benchmark against your peers in real time.
- Utilize reports to negotiate contracts and other professional opportunities.
- Utilize reports to demonstrate competency of new skills.
- Evidence of ongoing self-assessment and performance improvement activities
- Take steps to improve performance in a timelier basis.
- Utilize AQuIRE reports as evidence of participation in performance improvement activities for maintenance of certification.
- Initiate research projects utilizing data only aggregated through AQuIRE.
- Gain opportunities for recognition in manuscripts based on AQuIRE data.

Fellows-in-training can:

- Self-assess their practice and demonstrate competency over time.
- Identify gaps in knowledge and practice, and engage in targeted educational interventions.
- Develop performance improvement projects.

Do I Need IRB Approval To Participate?

The need for IRB approval to participate in a quality improvement registry is at the discretion of your individual IRB. AQuIRE is HIPAA-compliant and is for the purpose of receiving feedback about your clinical performance and, therefore, patients' personal health information is not required in either of the bronchoscopy registries. Furthermore, a business associate agreement has been developed for participating sites and must be agreed to before data entry is permitted.

How Do I Enroll?

The AQuIRE Bronchoscopy Module will be open to ACCP Members in early 2010. To enroll, contact Joyce Bruno Reitzner, MBA, MIPH, at jbruno@chestnet.org or by calling (847) 498-8120. ■

This Month in *CHEST*: Editor's Picks

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

- **Pneumothorax After Air Travel in Lymphangioleiomyomatosis, Idiopathic Pulmonary Fibrosis, and Sarcoidosis.** *By Dr. A. M. Taveira-DaSilva, et al.*
- **Biomarkers of Heart Failure in Pleural Fluid.** *By Dr. J. M. Porcel, FCCP, et al.*
- **Role for Interleukin-6 in COPD-Related Pulmonary Hypertension.** *By Dr. A. Chaouat, et al.*
- **Revisiting Stage IIIB and IV Non-small Cell Lung Cancer: Analysis of the Surveillance, Epidemiology, and End Results Data.** *By Dr. W. N. William, Jr., et al.*
- **Chronic Bronchitis, COPD, and Lung Function in Farmers: The Role of Biological Agents.** *By Dr. W. Eduard, et al.*
- **Statins in COPD: A Systematic Review.** *By Dr. S. Janda, et al.*

INTERACTIVE PHYSIOLOGY GRAND ROUNDS

- **A 22-Year-Old Woman With Unexplained Dyspnea.** *By Dr. E. Hekier; and Dr. J. Mandel.*

COMMENTARY

- **What Went Right: Lessons for the Intensivist From the Crew of US Airways Flight 1549.** *By Dr. L. A. Eisen, FCCP; and Dr. R. H. Savel.*

www.chestjournal.org

NetWorks

Global Pulmonary Vascular Disease, Lung Donor Pools

Affiliate

Implications From the Institute of Medicine Report on Resident and Fellow Duty Hours

In response to a congressional request, the Institute of Medicine (IOM) recently issued its recommendations for revisions to the current duty hours restrictions for trainees in graduate medical education programs. These recommendations for revisions can be found at www.iom.edu/?ID=60449. The IOM report focuses on the impact of sleep deprivation and fatigue on medical errors and calls for more stringent restrictions on work hours and schedules for residents and fellows. Highlights of the recommendations include the following:

- ► No change in the 80-h maximum work week or 30-h maximum shift length
- ► Shifts longer than 16 h and overnight on-call duties must include a 5-h break for sleep between 10:00 PM and 8:00 AM.
- ► In-hospital night shifts may not exceed four consecutive nights.
- ► Minimum of 1 day (24 h) off per week (no averaging) *plus* one 48-h period off per month (a minimum of 5 days/month)
- ► External moonlighting must be included and is subject to duty hour limits.

At this time, few critical care medicine and pulmonary fellowship programs have overnight call. However, other restrictions could significantly alter the activities of current fellows. The IOM report acknowledges potential problems from more frequent handovers but provides little evidence that these new restrictions will result in fewer medical errors.

The IOM report includes a cost analysis that estimates a cost of $1.7 billion to implement these recommendations. Significant pressure now lies on the Accreditation Council for Graduate Medical Education, as practical solutions are necessary to ensure effective training and patient safety, while preserving professional self-regulation by warding off federal legislation.

Dr. John (Jack) Buckley, FCCP
Affiliate NetWork
Vice-Chair

Pulmonary Vascular Disease

The Pulmonary Vascular Disease NetWork is collaborating with the Pulmonary Vascular Research Institute (www.pvri.info), and several projects have been envisioned. The first is a special supplement to the *CHEST* journal to be published in 2010. This supplement will present a global perspective on pulmonary vascular diseases and, more specifically, pulmonary hypertension (PH). Physicians in the United States often assume that idiopathic PH and collagen vascular disease cause the majority of pulmonary vascular disease in the world. However, recent statistical estimates indicate that the majority of pulmonary vascular disease in the world is caused by schistosomiasis and other entities, such as hemolytic anemias.

This special supplement will focus on causes of PH commonly seen around the world, especially in less-industrialized countries. These causes include schistosomiasis, congenital heart disease, high altitude and hypoxia, COPD, HIV, and hemolysis-induced pulmonary vascular disease. Special reports will be included from Pulmonary Vascular Research Institute task forces in China, India, the Middle East, and Latin America.

The supplement will be followed by a special symposium held at the CHEST 2010 meeting in Vancouver, BC, Canada. The discussion will address the challenges of recognizing and treating pulmonary vascular disease in the Third World, where PH-specific therapies are either not approved or prohibitively expensive.

The Pulmonary Vascular Disease NetWork hopes to bring readers of the *CHEST* journal and attendees of the CHEST meeting an international view of disease and mortality in PH.

Dr. Kamal Mubarak, FCCP
Pulmonary Vascular Disease NetWork
Chair

Thoracic Oncology

This has been another productive year for the Thoracic Oncology NetWork. The NetWork completed a project that explored the variation in experts' beliefs about lung cancer growth, progression, and prognosis. This brief report appeared in the *Journal of Thoracic Oncology* in April 2008. A second phase of this study surveyed Thoracic Oncology NetWork members about their understanding and

Continued on following page

Continued from previous page

beliefs of the biology of lung cancer and how it may affect the way they manage patients. The results of this survey are currently being analyzed for publication.

The NetWork also has been busy assembling the content for the CHEST 2009 program. Some of the scheduled topics are "Early-Stage Lung Cancer: Moving Beyond TNM Staging in the Era of Molecular Prognosis and Prediction," "Five Papers That Will Change How You Practice," and "Thoracic Oncology Interactive Tumor Board." Dr. W. Michael Alberts, FCCP, will chair the lung cancer guidelines update session, "What's Stage III?" In addition, a post-graduate course on lung cancer will be lead by the immediate past chair of the Thoracic Oncology NetWork, Dr. Gerard Silvestri, FCCP. The Thoracic Oncology NetWork open meeting will be held on Monday, November 2, 2009, at 8:00 AM and include a presentation by Dr. Farhood Farjah titled, "Outcomes-Based Research in Lung Cancer."

In addition, the Thoracic Oncology NetWork is currently collaborating with the Society of Thoracic Surgeons on a project to develop a consensus statement titled, "Management of High-Risk Stage I NSCLC Patients."

If you have ideas for topic submission for CHEST 2010, please contact any of the steering committee members via our NetWork Web site at www.chestnet.org/networks. To find out more about how to become involved with the Thoracic Oncology NetWork, contact Jenny Nemkovich at nemkovich@chestnet.org.

Dr. John A. Howington, FCCP
Thoracic Oncology NetWork
Chair

Transplant

Expanding the Donor Pool: Lung Transplant From Non-Heart-Beating Donors

Donor shortage is a major problem for all solid organ transplantation, especially lung transplantation, which continues to have the highest waiting list mortality compared with other organ transplants (Christie et al. *J Heart Lung Transplant* 2008; 27:957). In order to expand the pool of potential donors, a growing number of transplant centers are beginning to use non-heart-beating donors or donation after cardiac death (DCD), particularly for abdominal transplantation (Bernat et al. *Am J Transplant* 2006; 6:281).

Although the first lung transplant surgery performed in 1963 used donor lungs from a non-heart-beating donor (Hardy et al. *JAMA* 1963; 186:1065), it was not until recently that DCD donors have been more widely considered for lung transplantation. Most of the lung donors used in the last 3 decades were traditional brain-dead donors, and the use of DCD lungs has been slow to gain widespread acceptance.

Over the last several years, a few transplant centers around the world have begun to use controlled DCD (Maastricht category III) donors, who have a grave neurologic prognosis but do not meet the strict definition of brain dead. In 2002, only one lung transplant in the United States was from a DCD donor; however, the number of centers using DCD donors has progressively increased since that time. In 2008, 20 lung transplants were performed using DCD donors. The numbers continue to rise, as 13 DCD lung transplants were performed in the first 4 months of 2009, according to data from the United Network for Organ Sharing (UNOS) Registry.

The outcomes from DCD donation have primarily been series of case reports, which have been encouraging, with at least equivalent short-term outcomes compared with traditional brain-dead donors. Mason and colleagues (Mason et al. *J Thorac Cardiovasc Surg* 2008; 136:1061) recently reviewed the US experience with outcomes from 36 DCD lung donors and reported a 1-year survival of 94% and a 2-year survival of 87%. Data presented at The International Society for Heart & Lung Transplantation meeting in April 2009 (Kang et al. *J Heart Lung Transplant* 2009; 28:S149) demonstrated that bronchoalveolar lavage fluid from DCD donors compared with traditional brain-dead donors had lower levels of inflammatory cytokines, which may be associated with better short-term clinical outcomes after transplantation.

Overall, the early experience from the use of DCD donors in lung transplantation has shown that results are at least as good as those attained with conventional donors. Increased use of DCD donor lungs has the potential to ameliorate the organ shortage and further decrease the number of deaths on the lung transplant waiting list.

Dr. David Zaas, FCCP
Transplant NetWork
Steering Committee Member

PCCU Lessons This Month

▶ **Interventional Pulmonology.**
By Dr. Harman S. Paintal; Dr. Jürgen Hetzel; and Dr. Ganesh Krishna, FCCP
▶ **Sepsis: Definitions, Epidemiology, Etiology, and Pathogenesis.**
By Dr. Jonathan M. Siner

PCCU
PULMONARY AND CRITICAL CARE UPDATE
www.chestnet.or/education/online/pccu/index.php

Women's Health NetWork Luncheon and Open Meeting

The Women's Health Network invites CHEST 2009 attendees to attend the WHN Luncheon on Tuesday, November 3, 2009, at 11:45 AM to 1:00 PM, and the WHN Open Meeting immediately following from 1:00 PM to 2:15 PM.

Keynote speaker Dr. Michael Zack, FCCP, will present *Poetry and Medicine: The Case for Humanism in Science*. The WHN Luncheon is supported exclusively by an educational grant provided by Merck & Co., Inc.

The WHN Open Meeting will review the past year's accomplishments and consider opportunities for the AMA Alliance Screen Out! Collaboration, as well as feature last year's Clinical Research Award in Women's Health recipients and their projects. Dr. Subani Chandra, will present on her project – *Investigation and Correction of Gender Disparity in Chest Compression Technique During CPR*; and Dr. Margaret A. Pisani, FCCP, will present on her project – *Gender Differences as They Relate to Outcome in an Older ICU Cohort*. ■

Product of the Month

ACCP-SEEK XIX, Pulmonary Medicine JUST RELEASED—Order at www.chestnet.org or purchase at CHEST 2009!

ACCP-SEEK is designed to stimulate and challenge the learner's clinical thought processes regarding recall, interpretation, and problem-solving skills. The case-based questions contain histories, laboratory results, and images, and they provide education concerning current diagnostic and treatment strategies. Each volume contains questions, answers, and rationales. The rationales provide thorough explanations and reasoning for the correct and incorrect answers. The ACCP-SEEK series is used most commonly as an invaluable study tool for physicians interested in certifying and recertifying in sleep, pulmonary, and critical care subspecialties. ■

Sleep Disturbances May Provide Entry Into PTSD Care

Less stigma is attached to seeking help for a sleep disturbance than for a mental disorder.

BY SUSAN LONDON
Elsevier Global Medical News

SEATTLE — Returning military veterans with post-traumatic stress disorder often also have sleep disturbances that may provide an alternative, stigma-free entry into medical care, Anne Germain, Ph.D., said at the annual meeting of the Associated Professional Sleep Societies.

Approximately 1.6 million people have been deployed to Afghanistan and Iraq as part of the current combat operations in those countries, noted Dr. Germain, an assistant professor of psychiatry at the University of Pittsburgh.

Roughly one-third of these people have been deployed multiple times.

"We know that the risk of PTSD increases with each deployment," said Dr. Germain. "So whatever estimates that we have right now for PTSD, we are likely to see an increase with the number of deployments and duration of tours."

Deployment has been associated with an increased prevalence of PTSD, Dr. Germain noted. For example, 5% of Army personnel meet criteria for PTSD before deploying to Iraq, compared with almost 13% after their return, according to a study published in the New England Journal of Medicine (2004;351:13-22). In addition, it is known that three other psychiatric disorders—anxiety, depression, and alcohol misuse—become more prevalent after deployment.

"All of these disorders are associated with stigma," Dr. Germain observed.

"Despite the military's best effort to destigmatize mental health difficulties postdeployment, a lot of people will refuse or be very hesitant to seek care for these conditions," she noted.

However, all the disorders are also associated with sleep disturbances, including insomnia, irregular sleep-wake schedules, and hypersomnia. "Sleep disturbances may actually provide an entry into care that is not stigmatizing, that is more socially acceptable, that gets people to seek help first," she said.

When veterans with PTSD sleep in the lab, they sleep much better. They feel safe; somebody is watching them.

DR. GERMAIN

"And once they are in treatment, maybe we can address these other psychiatric difficulties."

When it comes to the pathogenesis of PTSD and sleep disturbances in returning military personnel, research has implicated both physical and psychological exposures during deployment, according to Dr. Germain.

Her team is specifically investigating the role of blast exposure in a new study that has thus far enrolled a total of 25 military veterans returning from Iraq or Afghanistan who reported having sleep difficulties.

Preliminary analyses have shown that the returnees had an average age of 28 years, and 92% were men. Forty percent had been exposed to a blast during deployment.

The prevalence of PTSD was higher in the group that was exposed to blasts than in the nonexposed group (90% vs. 67%).

The groups had nearly equal, moderate levels of insomnia as measured by mean scores on the Insomnia Severity Index, or ISI (16.5 vs. 16.0), and they also had the same poor sleep quality as measured by mean scores on the Pittsburgh Sleep Quality Index, or PSQI (10.7 vs. 10.7).

"These veterans are well within the realm for clinically significant sleep disturbance," Dr. Germain observed. "Those are levels of sleep disturbances that we treat."

However, the blast-exposed military veterans had a higher level of disruptive nocturnal behaviors, such as nightmares of traumatic events or dream enactments involving kicking or punching, as measured by mean scores on the PSQI Addendum (PSQI-A), a test which assesses sleep disturbances associated with PTSD (6.6 vs. 3.9).

"What these sleep disturbance findings mean is unclear at this time," she commented.

"But these findings are definitely something that we want to follow up, because the treatments for these types of sleep disturbances are very different from those that we typically use for insomnia, for example."

Both blast-exposed and -nonexposed returnees were similar in terms of sleep diary and polysomnography measures. However, she noted, the polysomnography data might have been confounded by the high prevalence of PTSD.

"When veterans with PTSD sleep in the sleep lab, they sleep much better. They feel safe; there is somebody watching them," Dr. Germain explained.

ALL POSTDEPLOYMENT MENTAL DISORDERS ARE TIED TO SLEEP DISTURBANCES, INCLUDING INSOMNIA, IRREGULAR SLEEP-WAKE SCHEDULES, AND HYPERSOMNIA.

"So usually they catch up on sleep a little bit, and their sleep efficiency is better."

Dr. Germain cautioned that definitive study results will require a larger sample size, as well as follow-up to assess the course of the sleep disturbances and PTSD.

A comparison of treatment outcomes in the blast-exposed and -nonexposed groups also will be needed, Dr. Germain said.

"I'm especially interested in looking at how sleep may play a role in the development of some of those mental health difficulties or adjustment difficulties—not just PTSD but other difficulties, too, such as depression—and in looking at the role of sleep in recovery as well," she said.

Dr. Germain reported that she had no conflicts of interest in association with her presentation. ■

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

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

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

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

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

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

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

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

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

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

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

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

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

Rx only

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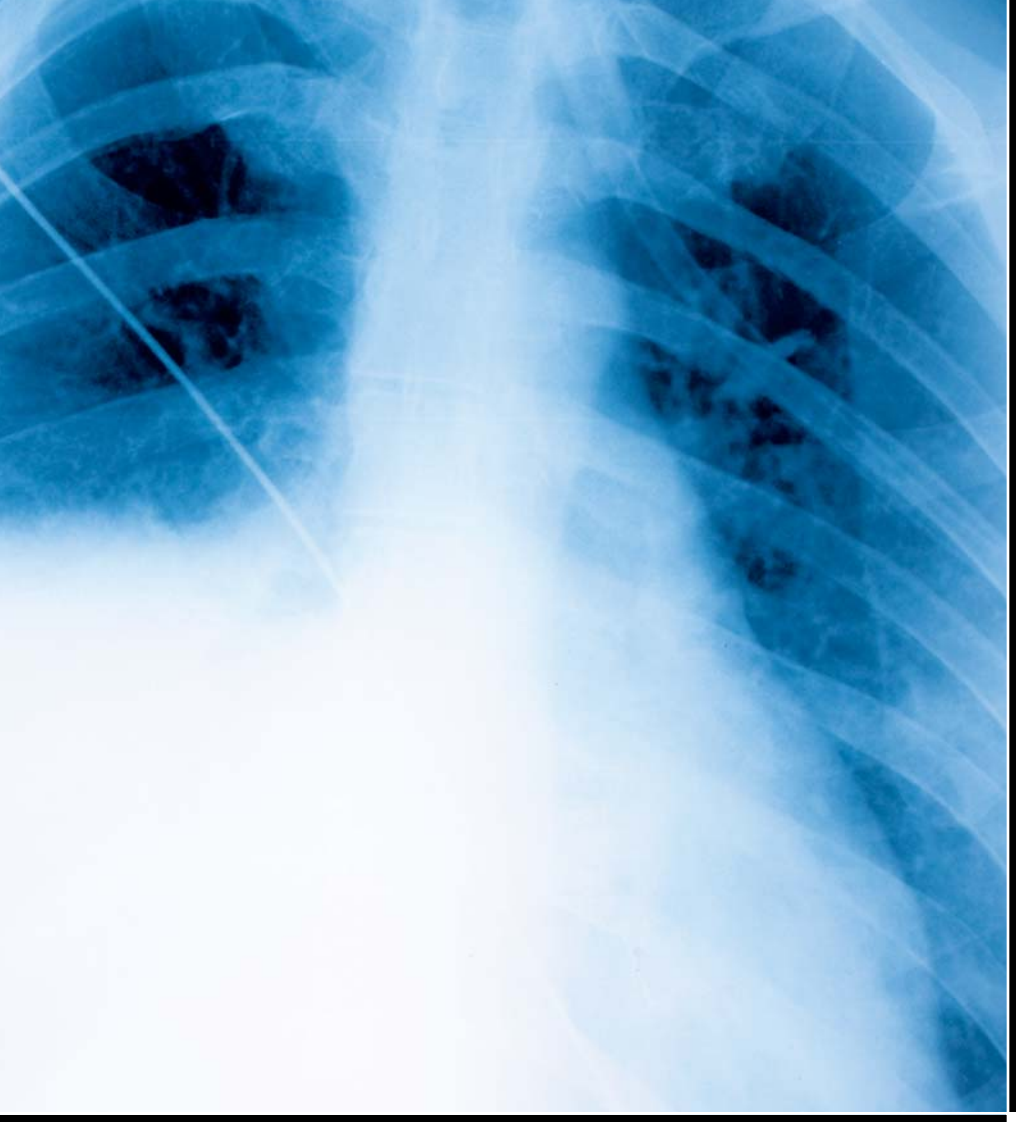

SERIOUS INFECTION

SERIOUS RESULTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IV/Oral
ZYVOX®
(linezolid)

SMART BUG. SMART DRUG.™

*Methicillin-resistant *Staphylococcus aureus*.

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

Please see brief summary of prescribing information on adjacent page.