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COURTESY DAN CEUSTERS

“There is enhanced care and satisfaction for everyone” when ICU patients receive palliative care, said Dr. Judith E. Nelson, FCCP.

Program Aims to Move Palliative Care to the ICU

BY MARY ELLEN SCHNEIDER

Elsevier Global Medical News

Critical care and palliative care may seem like opposing concepts, but experts in both fields say bringing palliative care techniques into the intensive care unit can decrease costs and improve patient satisfaction.

Now, a new project launched in partnership with the Center to Advance Palliative Care aims to jump-start the integration of palliative care techniques into ICU programs by providing a slew of online tools and resources.

The IPAL-ICU Project (www.ccapc.org/ipal-icu), which is partially funded by the National Institute on Aging, includes templates, protocols, quality monitoring tools, and a library of journal citations with the latest evidence about palliative care in the ICU. Through the new Web site, people can also learn how to contact ICU programs that have already integrated palliative care.

The first step for anyone

considering introducing palliative care into the ICU is to make the case to the multidisciplinary critical care team and to hospital leaders, said Dr. Judith E. Nelson, FCCP, the project director for the IPAL-ICU Project and a professor of medicine at Mount Sinai School of Medicine in New York City. But it's not a difficult case to make, she said.

“There is absolutely no downside here,” Dr. Nelson said. “There is enhanced care and satisfaction for everyone involved, and efficiencies for the institution and the health care system as a whole. It's really a win across the system, and there aren't that many places or strategies in health care that we can say that about.”

Research shows that the use of palliative care consultation programs has resulted in cost savings throughout hospitals, including reductions in ICU costs (*Arch. Intern. Med.* 2008; 168:1783-90). Those savings aren't achieved by increasing mortality, Dr. Nelson said.

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Pulmonary Endarterectomy Safe, Effective

Surgery beneficial in CTEPH patients.

BY MITCHEL L. ZOLER
Elsevier Global Medical News

TORONTO — Nearly 400 patients with newly diagnosed chronic thromboembolic pulmonary hypertension underwent pulmonary endarterectomy with a low, 5% in-hospital mortality rate at 17 European centers.

“In specialized centers, the surgical management of incident, newly diagnosed chronic thromboembolic pulmonary hypertension [CTEPH] provided favorable results as indicated by a low operative mortality and improvement of exercise capacity and hemodynamics,” Dr. Eckhard Mayer said at the annual meeting of the American Association for Thoracic Surgery.

“As low exercise capacity and high pulmonary vascular resistance are risk factors for survival, earlier diagnosis seems mandatory, and referral

to pulmonary endarterectomy surgery at expert centers should not be delayed,” said Dr. Mayer, director of the department of thoracic surgery at the Kerckhoff Klinik in Bad Nauheim, Germany.

The 1-year mortality rate among the 386 patients who underwent pulmonary endarterectomy was 7%.

The European CTEPH registry began in 2006, and the current review included 679 patients diagnosed during February 2007–January 2009. All patients included in the review had been diagnosed within 6 months of entering the registry, and none had received treatment for pulmonary artery hypertension before the CTEPH diagnosis. All patients received at least 3 months of anticoagulation therapy.

The consulting surgeons determined that 427 of the 679

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RSV Prevention Under Review

BY SHARON WORCESTER

Elsevier Global Medical News

ATLANTA — In the wake of a recent Food and Drug Administration advisory panel vote against recommending licensure of a new drug for the prevention of respiratory syncytial virus, a Centers for Disease Control and Prevention

working group on RSV immunoprophylaxis will continue to develop recommendations for the use of currently available products, the group's chair said.

The new drug currently under FDA review is motavizumab (MedImmune/AstraZeneca), a humanized monoclonal antibody. The FDA advisory panel expressed

concern that the drug has additional safety issues but no clear benefit over existing products on the market, Dr. Lance Chilton reported at a meeting of the CDC's Advisory Committee on Immunization Practices.

Efforts will continue to develop recommendations for prophylaxis, based on available

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**CRITICAL CARE
COMMENTARY**
Today, ECMO is safer and
easier to provide.

See page 9.

Procedure Has Low Mortality

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patients were operable, and 373 underwent surgery. The surgeons deemed the remaining 252 patients inoperable; despite that, 13 had surgery.

The median age of the 386 surgery patients was 60, and 54% were men. The average time from their first symptoms until diagnosis was 15 months, and 80% had a prior episode of acute pulmonary embolism. Their median pulmonary artery pressure at rest was 48 mm Hg, and median pulmonary vascular resistance (PVR) at rest was 728 dyn/sec/cm⁵. About a quarter of the patients received treatment for pulmonary artery hypertension following the diagnosis.

The surgical technique used followed the approach developed at the University of California, San Diego, with complete endarterectomy done in 358 patients; 143 received a perioperative vena cava filter. During surgery, patients spent a median of 35 minutes in deep hypothermia circulatory arrest.

Surgical complications occurred in 49% of patients. The most common complications included infection in 19%, persistent pulmonary hypertension in

17%, and neurologic complications in 11%. Several patients had more than one complication.

A multivariate regression analysis identified two baseline risk factors with a statistically significant link to mortality. PVR at baseline was associated with both in-hospital and 1-year mortality. Patients with a baseline PVR of less than 400 dyn/sec/cm⁵ had no increase in in-hospital mortality and a 2% increase in 1-year mortality, compared with those with a baseline PVR of 1,200 dyn/sec/cm⁵, who had a significant 11% increase in in-hospital and a 13% increase in 1-year mortality. Each 100 dyn/sec/cm⁵ increase in PVR boosted the in-hospital mortality rate by 79% and the 1-year mortality rate by 40%.

Six-minute walk distance was tied to 1-year mortality only. Each 100-m additional distance walked in 6 minutes

COMMENTARY

Dr. Joseph Barney, FCCP, comments: This article illustrates how this modality of treatment for selected patients with severe dyspnea and disability from embolic disease has developed into a more mainstream treatment. Centers with cardiothoracic surgeons and supporting subspecialists experienced in the care of patients during and after this

procedure in the United States are currently recapitulating the outcomes seen in this European registry. Clearly, more exposure and information about the technique among physicians caring for patients with CTEPH will enhance physicians' knowledge about management of this disorder and referral to centers that provide this service.

reduced the 1-year mortality rate by 60%.

Patient volume at individual centers also showed a relationship with mortality, but the differences among the various levels of patient volume were not statistically significant. At the six centers that treated 1-10 patients per year, in-hospital mortality averaged 7% and 1-year mortality was 11%. At the eight centers that treated 11-50 patients per year, in-hospital mortality averaged 5% and 1-year mortality was 7%. The three centers with an annual volume of more than 50

patients had an average in-hospital mortality of 4% and a 1-year mortality of 5%.

Pulmonary endarterectomy generally led to substantial improvements in PVR and New York Heart Association functional class. Prior to surgery, PVR averaged 736 dyn/sec/cm⁵. Immediately after surgery it averaged 248 dyn/sec/cm⁵, and 1 year later it remained at an average of 235 dyn/sec/cm⁵. Prior to surgery, three-quarters of the patients had NYHA class II or IV function; after surgery, 87% had class I or II function. ■

CDC Drafting Recommendations

RSV • from page 1

information on disease burden, safety, efficacy, and economics, said Dr. Chilton, chair of the RSV immunoprophylaxis working group and a pediatrician with the Young Children's Health Center at the University of New Mexico, Albuquerque.

RSV is the leading cause of lower respiratory tract illness in infants and young children, and currently there is no vaccine available, Dr. Chilton said, noting that efforts to develop a vaccine are ongoing, and "when it comes, it will change the face of pediatrics."

Until then, preventive treatment is available in the form of palivizumab—a safe and effective product for immunoprophylaxis, according to Dr. Chilton. However, the drug is expensive, with an

estimated cost of nearly \$6,700 per patient per year, and guidelines for appropriate use are needed, he said.

EFFORTS TO DEVELOP A VACCINE ARE ONGOING, AND 'WHEN IT COMES, IT WILL CHANGE THE FACE OF PEDIATRICS.'

Dr. Chilton said the working group's efforts to develop such guidelines will include:

► A review of the epidemiology of RSV infection, including seasonality and host

and environmental risk factors for severe disease.

► A review of the safety and efficacy of prophylaxis.

► An assessment of the costs and benefits of prophylaxis.

► Identification of the areas requiring further research for informing recommendations.

► Drafting of recommendations for ACIP consideration.

Up to 125,000 hospitalizations for RSV occur in the United States each year, with the highest incidence in young infants, and with a disproportionate burden among those with lung disease, heart disease, or prematurity.

The FDA is currently scheduled to review the biologics licensing application for motavizumab this month.

Dr. Chilton reported that he has no financial conflicts of interest relevant to his presentation. ■

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Reported Infection Rates Not Tied to ICU Mortality

Hospital infection reports provide limited data regarding quality of care and mortality.

BY CRAIG GUILLOT
Elsevier Global Medical News

NEW ORLEANS — A hospital's reported rate of infections acquired in the intensive care unit may not be an indication of ICU mortality risk.

The finding that these publicly reported infection rates often are not tied

THIS STUDY 'CHALLENGED A COMMONLY HELD ASSUMPTION. ... USING THESE REPORT CARDS TO CHOOSE A HOSPITAL MAY BE MISLEADING AND HARMFUL.'

to patient outcomes shows that the data can be misleading and may not be a measure of overall ICU performance, according to researchers who conducted a retrospective study presented at an international conference of the American Thoracic Society.

The study included 158 hospitals in Pennsylvania linked in 2006 to the state Department of Health's 30-day mortality data. The data included 18,544 ICU admissions involving mechanical

ventilation and 16,285 admissions involving central venous catheterization.

Within the two cohorts, the data were extrapolated to derive a risk-adjusted ICU mortality rate for every hospital in the analysis, which controlled for variables such as severity of illness, age, and gender, reported Dr. Kate Courtright of the University of Pennsylvania, Philadelphia.

The results showed no correlation between risk-adjusted mortality and publicly reported ICU infection rates. Many hospitals with few pneumonia or catheter-associated bloodstream infections had higher ICU mortality than did hospitals with high infection rates. The 43 hospitals that reported no cases of ICU-acquired pneumonia had a mortality rate of 35.7% for patients on mechanical ventilation, but hospitals with high infection rates (1-8 infections per 1,000 ventilator-days) had an average mortality of 34.6%.

Median risk-adjusted mortality was 26.9% for catheterized patients and 35.1% for ventilated patients. In linear regression models adjusting for hospital size and academic status, higher ventilator-associated pneumonia rates were not associated with higher risk-adjusted mortality in ventilated patients.

Similarly, higher catheter-related bloodstream infection rates were not associated with higher risk-adjusted mortality in catheterized patients, reported Dr. Courtright.

"We found there was essentially zero correlation in the mechanical ventilation cohort and catheter group of patients. There wasn't even a trend," she said.

Health care-associated infections (HAIs) affect 5%-10% of hospitalized patients in the United States, resulting in an estimated 90,000 deaths annually. Public reporting of HAI rates has increased in recent years, and 29 states now have mandatory reporting laws, Dr. Courtright said.

The commonly held but unproven assumption has been that hospitals with lower rates of HAI have higher quality of

care and lower patient mortality. But this study showed that hospital infection reports provide limited data regarding quality of care and mortality, she said. Many hospitals with otherwise good report cards may have high mortality, and thus many good performers may be penalized for their reported infection rates. This is especially important because infection rates will be used as a measure for hospital reimbursement and "pay for performance" incentives under health care reform.

This study "really challenged a commonly held assumption. Many performance initiatives are based on public data, and using these report cards to choose a hospital may be misleading and harmful," she said.

Dr. Courtright reported no conflicts of interest. ■

COMMENTARY

Dr. Carl Kaplan, FCCP, comments:

This is outstanding work by the Pennsylvania physician who provides insight and reflects on the quality of the data that are offered to us for decision making and how this information will impact how our health-care dollars and limited resources are used in this country. This study may suggest that hospital public reporting and "report cards" are data that perhaps are

nurtured for hospital systems' branding and marketing. This is in sharp contrast to the primary intent of the process—and therefore may not lead to enhanced patient safety and quality of care, or to improved effectiveness and efficient delivery of care. Neither our patients, the communities we serve, the nation as a whole, nor the clinicians who provide patient-centered care benefit from the current process.

Integrating Care

Palliative • from page 1

Instead, the better communication fostered by using palliative care strategies results in a reduced use of non-beneficial ICU treatments and even a decreased length of stay. "It cuts back on delay and improves communication," Dr. Nelson said.

Right now, the biggest barrier is convincing people to let go of the old model of sequential care, Dr. Nelson said. In that model, a patient receives aggressive care in the ICU and, when that is exhausted, moves to palliative care in a hospice setting.

There's a fear that the introduction of palliative care early on means that the intensive care will somehow be diminished, she noted. "That's not necessary, and it's not optimal," Dr. Nelson explained. When done right, palliative care should support an aggressive care plan by making sure it is tailored to the patient's needs and desires. Palliative care can also help identify untreated pain and other symptoms.

Over the last decade, palliative care programs in general have spread across the country and increasingly been embraced by physicians. Dr. Nelson said she hopes that palliative care in the ICU setting will have similar success. "The goal here is to make this a routine part of critical care practice across the full range of ICUs," she said.

The concept of palliative care in the ICU is already catching on, noted Dr. J. Randall Curtis, FCCP, professor of medicine at the University of Washington and head of the section of pulmonary and critical care medicine at Harborview Medical Center in Seattle. Just a

few years ago, many people thought the very idea was crazy, he said—but he doesn't hear that anymore.

"I think people are still struggling with how to do it well, but I think there's a common acceptance that this is an important part of critical care," said Dr. Curtis, who is the immediate past president of the American Thoracic Society and a member of the IPAL-ICU advisory board.

Although acceptance is growing, ICUs can be a difficult place to integrate palliative care for several reasons, Dr. Curtis cautioned.

For one thing, critical care units are busy places, he said. Physicians and nurses working there need to balance considerations such as providing supportive palliative care against the need to focus on reducing central line infections and using ventilators appropriately. In addition, palliative care isn't the primary goal in the ICU—so the clinicians there need training on how to provide both types of care at the same time.

Another potential pitfall can be a "clash of cultures" between the ICU team and palliative care consultants, Dr. Curtis said. Palliative care specialists need to learn about the culture of the ICU, he cautioned, or they risk coming in with the attitude that the critical care team is being overly aggressive in their approach to some patients. That can happen if they don't understand the outcomes of conditions commonly treated in the ICU, such as severe chronic obstructive pulmonary disease, he said.

Palliative and critical care teams need to operate on the same page, agreed Dr. Daniel E. Ray, FCCP, director of the palliative medicine fellowship program at the Lehigh Valley Health Network in Allentown, Pa., and a member of the advisory board for the IPAL-ICU

Project. Otherwise, it is possible that patients and families could receive conflicting recommendations from providers.

The IPAL-ICU Project resources should go a long way toward helping institutions get started, Dr. Ray said. However, he cautioned that the resources should be customized to the unique culture of each hospital, and that leaders need to work on getting buy-in from everyone on the team to ensure that the templates are actually used.

Dr. Ray advised anyone interested in integrating palliative care into the ICU to attend a course sponsored by the Center to Advance Palliative Care. He also suggested connecting with an institution that has already integrated palliative care into the ICU. Look for a hospital with similar qualities, whether that's a community hospital or an academic medical center, he said. Dr. Ray is the Vice-Chair of the ACCP Palliative and End-of-Life Care NetWork. ■

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: Many intensivists have long embraced a role for end-of-life and palliative care. This has fostered programs and a network within the American College of Chest Physicians focused on achieving these goals. The IPAL-ICU Project outlined here aims to expand upon this initial work by bringing additional protocols and tools to the table. The project's Web site will also offer the ability to connect with ICU programs that have successfully implemented ICU palliative care. I believe the success of this endeavor will be enhanced through these connections and through building upon the foundations established in this area over the past decades. This is an important area for our patients.

Early Palliative Care Boosts Lung Cancer Survival

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

CHICAGO — Patients who began receiving palliative care when diagnosed with metastatic lung cancer lived longer, were less depressed, and had better quality of life than did their counterparts who received only standard care in a randomized phase III clinical trial.

The survival improvement was unexpected, as survival was not an end point of the study. The finding challenged the traditional paradigm in which palliative care is offered only after treatment options are exhausted. Moreover, the improvement occurred despite less-aggressive end-of-life care and longer hospice stays in the intervention arm of the trial.

Patients randomized to early palliative care lived a median of 11.6 months vs. 8.9 months in the control group ($P = .02$), Dr. Jennifer Temel reported at the annual meeting of the American Society of Clinical Oncology. After controlling for age, sex, and ECOG performance status, the adjusted hazard ratio was 0.59 ($P = .01$).

"It clearly shows that palliative care and active cancer therapy can go hand in hand," Dr. Raffit Hassan, a senior investigator at the National Cancer Institute, said in an invited discussion of the trial. He noted that it was the first randomized study of early palliative care

in newly diagnosed lung cancer patients and called for more randomized studies with survival as a primary end point.

Patients were eligible for the trial within 8 weeks of diagnosis with metastatic lung cancer if they had an ECOG performance status of 0-2, could read and answer questions in English, and planned to receive care at the tertiary care institution where the study was conducted. From June 2006 to July 2009, 283 patients were screened, but 59 declined to participate, 60 were not invited to participate, 9 were excluded, and the study closed while 4 others were eligible.

That left 151 patients who were randomized to early palliative care (77 patients) or standard care (74 patients). Both groups had a median age of 65 years and were similar with respect to sex, race, and marital status. In response to an audience question, Dr. Temel said the lines of chemotherapy were also identical.

The protocol called for patients in the intervention arm to meet with the palliative care team within 3 weeks of consenting to the trial and at least once a month thereafter; patients in the control arm also could receive palliative care, but by request of the patient, family members, or oncology clinician. While most standard care patients did not see the palliative care team within 12 weeks of entering the trial, 88% of the palliative arm had at least three visits by that point.

Dr. Temel, of Harvard Medical School and Massachusetts General Hospital in Boston, emphasized that "the nature of palliative care visits were not scripted or prescribed." The team addressed education about lung cancer treatment, symptom management, stress, decision making, and coping, as needed.

By the 12-week benchmark when psychological distress was measured, 27 patients had died: 10 in the standard

care arm and 17 given palliative care. In addition, 10 standard care and 7 palliative care patients did not complete the trial. All were followed until death. Dr. Temel said only 10 were still alive at the time of her presentation.

Depression in the palliative care patients was significantly less at 12 weeks, compared with standard care



Patients who received early palliative care lived a median of 11.6 months vs. 8.9 months in controls.

DR. TEMEL

patients, whether measured by the Hospital Anxiety and Depression Scale (38% vs. 16%, $P = .01$) or the more rigorous Diagnostic and Statistical Manual of Mental Disorders criteria for major depressive disorder (17% vs. 3.5%, $P = .04$), she said. Anxiety levels were not significantly different.

Quality of life also was better in the early palliative care cohort as measured by the FACT-Lung (91.5 vs. 98.0, $P = .03$) and FACT Trial Outcomes Index (59.0 vs. 53.0, $P = .01$) at 12 weeks. Indeed, both measures improved from baseline in the intervention arm, while declining among patients who received standard care.

More than half (54%) of patients in the standard care arm but only a third of the early palliative care group received aggressive end-of-life care ($P = .05$). The standard care patients were more likely to be admitted to a hospital or emergency department within 14 days of death (55% vs. 39%), spent fewer days in hospice (a median of 4 vs. 11), and were less likely to have documentation of their

resuscitation preferences (28% vs. 53%).

Dr. Temel suggested the better quality of life and reduced depression could be caused by better symptom management (along with illness acceptance further reducing depression). As for the gains in survival, she said the investigators hypothesized that it might be related to "earlier recognition and management of medical issues, improved quality of life and mood, less chemotherapy at the end of life, [and] longer hospice admissions."

Dr. Hassan noted and Dr. Temel acknowledged that the trial had a number of limitations, including the large proportion of patients who chose not to participate, a very small proportion with an ECOG performance status of 2, and lack of ethnic and racial diversity.

"What component of palliative care intervention resulted in beneficial effect is unclear," Dr. Hassan said.

The investigators are planning another study to address many of the questions raised, such as which services were most used and contributed to the improved survival. "We didn't know what we were going to find, so did not collect all the information needed," Dr. Temel said in an interview.

The current trial was supported by an ASCO Young Investigator Award, and the palliative care visits were covered by the patients' insurance, according to Dr. Temel. "We didn't have reimbursement issues; there may be state-to-state issues," she said.

Asked what prompted her interest in early palliative care, Dr. Temel explained, "The reason I chose to do lung cancer after my fellowship was I wanted to take care of ill patients and dying patients, and it didn't take doing it very long to realize we weren't doing a very good job of it."

Dr. Temel and Dr. Hassan disclosed no relevant conflicts of interest. ■

COMMENTARY

Dr. Paul A. Selecky, FCCP, comments: This is refreshing news in the light of the often dismal outcome in the treatment of metastatic lung cancer. Let this be a lesson to get our palliative care teams involved early in the course of this illness.

Monoclonal Antibody May Reduce Asthma Exacerbations

BY CRAIG GUILLOT
Elsevier Global Medical News

NEW ORLEANS — Long-term treatment with the monoclonal antibody omalizumab reduced the rate of asthma exacerbations by 25% in a phase IIIb, randomized, controlled trial of 850 patients with moderate to severe allergic asthma.

Researchers at five U.S. medical centers recruited patients, aged 12-75 years, who had had at least one asthma exacerbation in the past 12 months despite treatment with long-acting beta-agonists and an inhaled corticosteroid. The researchers added omalizumab (Xolair) to those medications in 427 study participants and placebo in 423.

Omalizumab (150-375 mg) or placebo was administered subcutaneously every 2-4 weeks,

with dosage and frequency determined by body weight and baseline serum total immunoglobulin E.

The primary outcome of the trial was the rate of asthma exacerbations during the 48 weeks of omalizumab treatment. Secondary outcomes included asthma symptom scores, asthma-related quality of life, and the daily number of puffs of rescue albuterol needed.

Of the 79% of recruits who completed the study, those receiving omalizumab had a rate of exacerbations of 0.66 at 48 weeks, while patients who received the placebo had a rate of 0.88, the team reported at an international conference of the American Thoracic Society.

The omalizumab patients also had a greater improvement

in asthma-related quality of life questionnaire scores, compared with placebo (1.15 vs. 0.92). While the mean number of rescue puffs per day and mean

THOSE RECEIVING OMALIZUMAB HAD A RATE OF EXACERBATIONS OF 0.66 AT 48 WEEKS, WHILE PATIENTS WHO RECEIVED THE PLACEBO HAD A RATE OF 0.88.

total asthma scores favored omalizumab, those two measures were not significantly different between the two groups after the researchers adjusted for multiple comparisons.

Adverse events occurred in 334 patients (79%) receiving placebo and 344 (81%) receiving

omalizumab. The most common adverse events in both the placebo and omalizumab groups were related to bleeding. There was one death in the placebo group due to cardiac arrest.

The percentage of serious adverse events was similar: 10.5% for placebo and 9.3% for omalizumab.

The current standard of care for patients with allergic asthma who do not respond well to inhaled corticosteroids is to add a long-acting beta-agonist or other medication. While previous clinical trials have suggested that omalizumab could be effective for these patients, the new trial "demonstrates that long-term treatment with omalizumab is safe and can significantly reduce the rate of asthma exacerbations ... in

patients with poorly controlled moderate to severe allergic asthma, despite receiving aggressive asthma controller therapy," the researchers concluded.

"This group did respond, and I think very selectively enrolling people who are on high doses of inhaled corticosteroid can validate the recommendations," said study coauthor Dr. William Busse, a professor of medicine at the University of Wisconsin, Madison.

The trial was funded by Genentech, a wholly owned member of the Roche Group. Dr. Busse disclosed that in the past 3 years he received consultancy assignments, advisory board appointments, and grants from several large firms, including Novartis, AstraZeneca, GlaxoSmithKline, Pfizer, and Merck & Co. ■

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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.

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG; and Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32(3):402-412. 2. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH; for Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25(3):980-992. 3. Boselli E, Breilh D, Rimmelé T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med*. 2005;33(7):1529-1533.

Please see brief summary on adjacent pages.



CONFIDENCE TO FACE COMPLEXITY

Biopsy Data Shed Light on Chemoresistant Lung Cancer

BY SARA FREEMAN
Elsevier Global Medical News

PARIS — Alterations in the expression of a well-known cancer gene called *Myc* may explain why some patients with non-small cell lung cancer are resistant to the effects of platinum-based chemotherapy.

The first results of a gene expression profiling analysis of NSCLC samples, taken prospectively from patients during

the BATTLE trial, were presented at the Worldwide Innovative Networking in Personalized Cancer Medicine Symposium.

"*Myc* is downregulated in treatment-refractory non-small cell lung cancer and may be an important factor in chemoresistance," said Dr. Pierre Saintigny, a clinical research fellow at the University of Texas M.D. Anderson Cancer Center in Houston.

"This observation has been validated *in vitro* in cell lines selected for cisplatin

resistance, and consistent with this observation *Myc* protein levels correlate with sensitivity to platinum-based agents in NSCLC cell lines," he added.

The clinical results of the phase II BATTLE (Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination) trial were reported recently at the American Association for Cancer Research meeting. These showed that selecting treatment based on a patient's individual tumor characteristics

was not only feasible, but also improved patient outcomes.

"This is a new kind of trial," Dr. Saintigny said. "It is biopsy driven, and patients had to have a mandatory biopsy with analysis of 10-15 biomarkers before inclusion in one of the four treatment arms."

The BATTLE trial involved 255 patients who were randomized to molecularly targeted treatment with erlotinib (Tarceva) alone or in combination with

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 [MDRSP¹]). **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 [MDRSP¹]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressor agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-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 postimplantation embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternbrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 14 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (V_{ss}) 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 40 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

bexarotene, sorafenib (Nexavar), or vandetanib, an experimental drug. All of the patients included in the trial had stage III/IV tumors and had been heavily pretreated with a variety of chemotherapeutic and molecularly targeted agents.

Core biopsy samples obtained from the patients were frozen and made available for further



'Oncogenic drivers, of which Myc is one, may be modified by systemic therapies.'

DR. SAINTIGNY

Gene expression profiling was generated using the U133 Plus 2.0 Array

analysis of gene expression. A total of 32 of these samples were assessed by Dr. Saintigny and his associates, and were compared with a control group of 45 lung samples taken from patients with stage III/IV tumors that had not previously been treated.

platform. Pathway and gene set analyses were used to identify networks and pathways associated with chemoresistance. Validation of the findings was performed in an independent set of cisplatin-sensitive cell lines using reverse phase protein array technology.

"The first study we did was to try to find some biologic features associated with chemorefractory



NSCLC," Dr. Saintigny said. A total of 3,963 probe sets were found to be differentially expressed between the BATTLE and the untreated NSCLC samples.

Some additional analyses showed that the expression of certain DNA repair genes was upregulated in the

BATTLE samples compared with the control samples, and that the expression of *Myc*, and of many of the genes it regulates, was downregulated.

Furthermore, *Myc* expression was associated with sensitivity to cisplatin.

These data suggest that the role of anticancer agents that specifically target *Myc* may need to be reevaluated, Dr. Saintigny suggested, and that the mechanisms behind the downregulation of the oncogene should be further explored.

"Probably the most important message is that oncogenic drivers, of which *Myc* is one, may be modified by systemic therapies," Dr. Saintigny observed. He proposed that these findings highlight the importance of doing biopsies in patients before they enter clinical trials to try to understand how such oncogenic drivers are altered by treatment.

Further analysis of the BATTLE samples will be undertaken, including testing of available gene expression signatures in relation to the primary end point of the study (8-week disease control) and the duration of progression-free survival in the four treatment arms.

"People talk a lot about personalized medicine, but this is the first time in a prospective clinical trial that a biopsy was mandated, analyzed for biomarkers, and then treatment was assigned based on the molecular defects," said Dr. Waun Ki Hong, professor of medicine and head of the division of cancer medicine at the M.D. Anderson Cancer Center.

"We used to treat lung cancer patients empirically with chemotherapy, but it is clear that the biologic behavior of each tumor can be different," Dr. Hong said. "The BATTLE data show that it is possible to target therapy according to the underlying genetic abnormality and thus represents the first real step in advancing personalized medicine."

Dr. Saintigny said he had no conflicts of interest. Dr. Hong is the principal investigator for the BATTLE project, which is supported by the U.S. Department of Defense.

values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

ADVERSE REACTIONS Adult Patients The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators* (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events† were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators‡ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events§ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections¶ with ZYVOX (n=248) or cefadroxil (n=251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocytopenia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 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 10³/mm³) 0.7 and 0.8; WBC (x 10³/mm³) 0.2 and 0.6; neutrophils (x 10³/mm³) 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 10³/mm³) 3.0 and 1.8; WBC (x 10³/mm³) 2.2 and 1.3 and neutrophils (x 10³/mm³) 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 10³/mm³) 0.0 and 0.4; WBC (x 10³/mm³) 0.8 and 0.8; neutrophils (x 10³/mm³) 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 10³/mm³) 12.9 and 13.4; WBC (x 10³/mm³) 12.4 and 10.3 and neutrophils (x 10³/mm³) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry¶ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections¶ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry¶ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see WARNINGS). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see PRECAUTIONS). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see PRECAUTIONS). Convulsions have been reported with the use of ZYVOX (see PRECAUTIONS). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

*MDRSep 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.

†††††>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

Rev. May 2008

Dr. W. Michael Alberts, FCCP, comments: "Personalized" therapy (or treatment tailored to the individual patient's tumor characteristics) has been shown to be not only feasible but also successful in improving outcomes. This very exciting and promising avenue of research has the potential to revolutionize the treatment of advanced-stage lung cancer.

FROM THE CEO

Weaving the Work of the ACCP and The CHEST Foundation

I have the distinct honor to serve as an officer on The CHEST Foundation Board of Trustees. This experience with the philanthropic arm of the ACCP has been one of my most

rewarding since becoming the Executive Vice President and CEO of the College last fall. At that time, ACCP leaders, staff, and I committed to advancing the College to the next level, including, and especially, The CHEST Foundation, which members have aptly described to me as the “soul of the ACCP.” The members understand that The Foundation, through its work in tobacco use prevention, humanitarian service, clinical research, and critical care/end-of-life care, adds an important human dimension to the College.

Specifically, the Board of Trustees sought to expand The CHEST Foundation fundraising base, with a measurable increase in donations. To that end, in January 2010, The Foundation engaged the consulting firm Cause Innovation to develop an innovative

fundraising and branding initiative. The initiative consisted of four phases: (1) internal and external analyses; (2) brand analysis and enhancement strategy; (3) development of a master strategy; and (4) resource identification and execution.



BY PAUL A. MARKOWSKI, CAE

To date, Cause Innovation, working collaboratively with CHEST Foundation staff and leadership, as well as with ACCP staff and leadership, has analyzed the resources and assets of the College and Foundation and crafted a master strategy. The firm conducted extensive and inclusive research to gain a thorough understanding of The Foundation and the ACCP and their relationship to one another and to our members. This phase included, but was not limited to, one-on-one interviews with leadership and an online survey of 1,000 members.

Based on its research and evaluation, Cause Innovation identified a need to break down walls between the ACCP and The CHEST Foundation. The ACCP Strategic Plan 2010 – 2011, which the Board of Regents approved

at its June meeting, deliberately weaves the work of the ACCP and The Foundation together to strengthen the College as a whole by, for example, incorporating the funding initiatives of each into a single division. Similarly, The Foundation’s master strategy, which we are currently refining, will integrate The Foundation into the ACCP brand to create a more compelling position that provides platforms for cause marketing, drives innovative fundraising strategies, and increases member engagement.

Eighty-three percent of Americans believe that companies have a responsibility to help support causes, 72% of Americans want their employers to do more to support a cause or social issue, and 80% of Americans want companies to address health issues through cause marketing (2007 Cone Cause Evolution & Environmental Survey). These statistics suggest the enormous potential of “strategic cause alliances”—unique, integrated marketing strategies to engage consumers, employees, vendors/suppliers, and other stakeholders in raising funds for

a cause, and in the case of The CHEST Foundation, to advance the prevention and treatment of chest diseases.

Keys to the success of The CHEST Foundation master strategy are the creation of a strategic architecture based on the attributes of The Foundation in the areas of education, care, and community; a microsite to establish a public face that leverages ACCP and Foundation assets related to patient education about the prevention of chest diseases; and a branding tag line that telegraphs the work of The Foundation to stakeholders. The Foundation will unveil more about its master strategy, including an implementation plan, identification of resources, and timeline, in the coming months.

Stay tuned as we continue to propel the ACCP and The CHEST Foundation, together, to the next level and, in so doing, realize the enormous promise that The Foundation holds as the soul of your ACCP. ■

MR. MARKOWSKI is Executive Vice President and Chief Executive Officer of the American College of Chest Physicians.

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Ambassadors Group Members Promote Lung Health

Ambassadors Group members; Monir Almassi, RN; and her daughter, Neda Almassi, organized the sixth annual 3K Walk/Run for Kids' Lung Health on May 19, 2010, at Wisconsin Hills Middle School (WHMS) in Brookfield, WI. This is just one of two annual events that Mrs. Almassi organizes. Due to her efforts, sixth grade students at Pilgrim Park Middle School (PPMS) in Elm Grove, WI, attended their fourth annual 3K Walk/Run for Kids' Lung Health on May 14, 2010.

CHEST Foundation staff members Sue Ciezadlo and Teri Ruiz attended the WHMS event and saw firsthand how 320 sixth graders were kept involved while learning about lung health. Utilizing information provided in The CHEST Foundation's Lung LessonsSM curriculum, two area high school students presented their “Lung Health” presentation to the children. Following this, Mrs. Almassi recapped the major points and stressed to the children the importance of lung health.

Then it was time to begin the 3K Walk/Run held in the streets neighboring WHMS. Mrs. Almassi had coordinated with teachers, parents, and the Brookfield Police Department to help along the course. Upon completing the course, each student received a Love Your Lungs® wristband and a “Teens and Tobacco” booklet from the Brookfield Police. Back inside, the children were able to get an up-close look at Mrs. Almassi's pig lung demonstration of diseased vs healthy



Monir (left) and Neda Almassi use props to show smoking's harmful effects.

lungs. She also had a “jar of tar” for the students to see how a year's worth of smoking pollutes the lungs. Mrs. Almassi answered questions and continued to stress the harmful effects of tobacco use.

The CHEST Foundation appreciates the dedication of Monir and Neda Almassi and their innovative use of the Lung LessonsSM curriculum. Because of their efforts, the middle school children at WHMS and PPMS are actively engaged in lessons that give them memorable images and

specific information about the dangers of smoking. Hopefully, these important messages will have a lifelong impact. The CHEST Foundation congratulates the Almassi family for establishing such an excellent lung health outreach tradition in their community. For more information about how you can implement an outreach program in your community, go to www.chestfoundation.org/foundation/ambassadors/tobacco.php. ■



Critical Care Commentary

It's Time To Reconsider Adult ECMO

Extracorporeal membrane oxygenation (ECMO) is a technology that provides long-term cardiopulmonary bypass support for patients with the most severe but potentially reversible forms of respiratory and/or cardiovascular derangements. This technology has a long history in modern medicine and has become the

standard of care for many childhood disorders. Early investigations of ECMO in the adult population demonstrated that it was an expensive, invasive modality that did not improve long-term outcome (Morris et al. *Am J Respir Crit Care Med.* 1994;149[2Pt1]:295; Zapol et al. *JAMA.* 1979;242[20]:2193). However, more recent data suggest that ECMO has a place in the treatment of the adult patient with severe respiratory failure (Peek et al. *Lancet.* 2009;374[9698]:1351; Davies et al. *JAMA.* 2009;302[17]:1888). Advances in ECMO technology suggest that the time is right for a renaissance in adult ECMO use.

The technology behind the ECMO circuit is simple in concept. The essential components include a pump, oxygenator, tubing, and vascular access (Fig 1). Each of the circuit components has undergone decades of refinement such that a modern ECMO circuit looks little like the systems of the past. Older circuits required frequent maintenance to the tubing to prevent malfunction, and the tubing was subject to occasional rupture or other catastrophic failure due to the roller pumps that were used. Constant attendance of the device by a trained technician was, therefore, mandatory. These problems limited ECMO use to a few centers and increased operational costs.

Recent advances and mass manufacturing of extracorporeal technologies have offered the opportunity to provide ECMO in a simplified and cost-effective manner. Such improvements include low resistance and highly reliable centrifugal pumps with minimal risk of failure. The older silicone-based oxygenators that suffered from regular plasma leak have been replaced by efficient, low-resistance polymethylpentene devices. The new generation of oxygenators operate at lower pressures than the older units, resulting in less hemolysis and lower circuit pressures. Importantly, the new oxygenators can support a patient for weeks without failure. Bedside monitoring of anticoagulation using the activated clotting time

point-of-care testing devices has been simplified with a shift to central lab-based activated partial thromboplastin times.

Vascular access has also undergone considerable enhancements. ECMO circuitry initially involved accessing the venous and arterial circulation through open surgical exposure of venous and arterial vessels. Blood

was extracted from the venous circulation, run through an oxygenator, and reinfused into a major artery, similar to cardiopulmonary bypass (Fig 1). Today, percutaneous techniques are commonly used for vascular access. The recent FDA approval of double-lumen adult venous cannulae (Fig 2) has simplified vascular access by allowing clinicians to use only a single venovenous (VV) cannula for support. These cannulae are designed to drain venous blood from the superior and inferior vena cava and then infuse highly oxygenated blood directly into the right atrium via a specially designed inflow port (Fig 1). This technique offers respiratory support with a reduced risk of ischemia and other complications associated with arterial-based access. Another advantage of the VV devices is their similarity to other large multilumen central venous catheters used in the ICU. The ECMO VV cannulae can be inserted by nonsurgical intensivists with additional training. VV ECMO is now the preferred method of support for adult patients with acute respiratory failure.

All of these advances have made ECMO considerably simpler and safer. Although the technology still has a considerable level of complexity, it no longer requires a dedicated team to provide continuous support at the patient's bedside. The modern ECMO system is simple enough that the nurse, with additional training on surveillance of the circuit and basic troubleshooting, can attend to both the patient and the ECMO circuit. Of course, this does not eliminate the need for the availability of knowledgeable and well-trained ECMO technicians. Such individuals are necessary to coordinate safe ECMO services, build and maintain ECMO systems, initiate and terminate ECMO support, and provide a higher level of ECMO troubleshooting than an ICU nurse could or should be expected to do.

Resistance to using ECMO for respiratory failure may linger from earlier and, arguably, no longer applicable studies. In 1979, 90 extraordinarily ill patients with

severe ARDS were enrolled in an NIH-sponsored, randomized, prospective trial of VA ECMO vs standard mechanical ventilation (Zapol et al. *JAMA.* 1979; 242[20]:2193). Forty-eight patients were managed using ECMO, and 42 received conventional ventilator support. The survival difference was not significant between the groups (9.5% vs 8.3%). A subsequent trial published by Morris and colleagues (*Am J Respir Crit Care Med.* 1994;149[2 Pt1]:295) of 40 patients with severe ARDS, 21 of whom were randomized to ECMO for CO₂ removal, showed no difference in survival between groups.

While it is important to recognize that the early trials of ECMO did not show a survival benefit, it is also important to acknowledge how standard management of ARDS and the critically ill has evolved since these trials. Low tidal volume strategies, goal-directed sepsis management, DVT prophylaxis, and central line placement are all far different today than they were even 10 years ago. Expected mortality for a variety of critical illnesses

ECMO support, and overall survival or severe disability at 6 months was 63% for the ECMO group vs 47% for the conventional management group. Appropriate criticisms of this study have focused on the lack of standardized management in the controls. Also, statistical significance was lost if patients from the ECMO center cohort who did not receive ECMO were removed. Many have reflected on CESAR as a trial of transfer of patients with severe ARDS to a comprehensive center with ECMO support rather than a trial of the ECMO technology itself.

However, the recent ECMO experiences with ARDS in the United Kingdom and severe respiratory failure due to influenza A(H1N1) have led to a renewed interest in using ECMO in adult respiratory failure. A report on ECMO and survival rates outside of the clinical trial environment was provided in *JAMA* (Davies et al. *JAMA.* 2009;302[17]:1888). In this study, conducted in Australia and New Zealand, 68 patients suffering from influenza A(H1N1) with ARDS and

treated with ECMO were evaluated. The patient population in the ECMO cohort was exceptionally ill, with a mean Pao₂ to Fio₂ ratio (P/F ratio) of 56 on an average of 18 cm H₂O of positive end-expiratory pressure prior to initiation of ECMO therapy. Follow-up communication reported that 17 patients died in hospital (Freebairn et al. *JAMA.* 2010;303[10]:941; author reply 942). Overall survival to hospital discharge among patients treated with ECMO was 75%—higher than reported with other series, which

may reflect a population with fewer comorbidities and a single pathologic condition (Bartlett et al. *JAMA.* 2000;283[7]:904).

ECMO today is far simpler and safer, and less technologic prowess and manpower are required at the bedside. In select populations, ECMO may provide a survival advantage in adults compared with traditional management. However, any institution interested in providing ECMO support must understand the high level of training and commitment required of all practitioners involved in the care of such patients. While ECMO is not considered the standard of care, recent advances suggest it is worthwhile to consider this approach when proven ventilation techniques are not adequate. ■

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Dr Andrew L. Rosenberg
Division of Critical Care
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University of Michigan Medical Center
Ann Arbor, MI



initially involved accessing the venous and arterial circulation through open surgical exposure of venous and arterial vessels. Blood

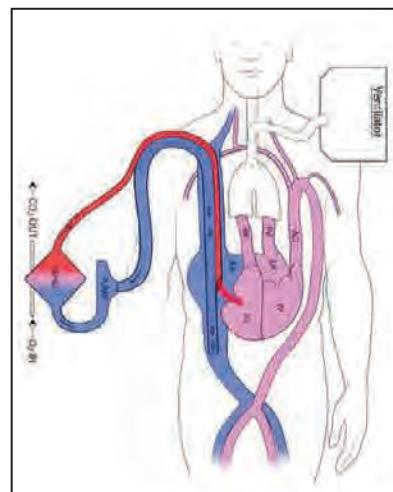


Figure 1. Basic components of an ECMO circuit.



Figure 2. Example of a double-lumen ECMO cannula.

IMAGES COURTESY DR. JAMES M. BLUM



DR. NEIL
HALPERN, FCCP
Section Editor,
Critical Care
Commentary

Resistance to using ECMO for respiratory failure may linger from earlier and, arguably, no longer applicable studies. In 1979, 90 extraordinarily ill patients with

was far higher in 1979 than expected today. These transitions in care of the patient with respiratory failure have made it exceptionally difficult to understand how ECMO may have actually impacted outcome during this period. Hence, more recent data may help illustrate the potential impact of the technology.

The first randomized trial data supporting the use of ECMO in the adult population were published in 2009 by Peak and colleagues (*Lancet.* 2009; 374[9698]:1351). The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial, through a minimization strategy, enrolled 180 patients with severe ARDS (Murray score > 3 or pH < 7.20). They were randomized to either care at a tertiary care center or transfer and management at a single ECMO center. Of the 90 patients randomized for transfer to the ECMO center, 5 died prior to or during transfer, and 16 improved with conventional management. Sixty-eight patients received

NETWORKS

Diversity, Travel Medical Insurance, Asbestos

Cultural Diversity

Diversity is about knowledge, respect, compassion, and consideration. It is about taking the “me, myself, and I” out of the equation and replacing those words with otherness. The Cultural Diversity in Medicine NetWork mirrors the diversity of the ACCP. In recent years, the NetWork has focused on diversity-related issues in end-of-life care, racial disparities in lung cancer, Latino-Hispanic demographics and health systems utilization, humanitarian aid, home care in rural populations, and the effects of race, gender, socioeconomic status, and sexuality on the ethical practice of pulmonary and critical care medicine.

Diversity is everpresent also in the activities of The CHEST Foundation. In 2009, awards were distributed for projects in Peru, Bolivia, India, and Jordan, as well as the United States. This year, 2010, is The Year of the Lung, and the ACCP is partnering with other international organizations to raise global awareness of lung health, urging policy makers to increase research funding, enhance wellness programs, and support environmental and air quality legislation.

Diversity is obviously of importance when ACCP members reflect on health reform, communication, and access to

care. Despite governmental funds devoted to studying and potentially correcting disparities, the economics of health care continue to create barriers to care. Diversity is the fabric of life. Culturally competent care requires that we nurture relationships with others in full recognition of our own potential biases and beliefs. As patient advocates, it is our responsibility to practice sensitively and knowledgeably, taking into account our cultural similarities, as well as differences. In the years ahead, the Cultural Diversity in Medicine NetWork intends to increase its membership and interact even more closely with other ACCP NetWorks. We hope you will join us at CHEST 2010 for our NetWork Open Meeting and Cultural Diversity in Medicine Luncheon. We invite you to let us know what we might do to assist you in your practices and educational endeavors by contacting the steering committee at networks@chestnet.org.

Dr Henri Colt, FCCP
Steering Committee Member

**Home Care: Getting Your Medical Act Together and Taking It on the Road**

The advent of more portable medical equipment has made international travel a reality for many disabled patients. In 2004, *The New York Times* reported that spending by American travelers with disabilities exceeds \$13.6 billion annually (Koeppel. *The New York Times*. www.nytimes.com/2004/02/17/business/17disabled.html. Accessed June 10, 2010). When

traveling internationally, it is important to purchase a short-term health policy designed specifically for travel outside home countries prior to travel.

Travel medical insurance is essential to safe, enjoyable travel. It provides coverage for medical expenses, including transportation to the hospital, physician services, hospital charges, operating rooms, and emergency medical evacuation. Most health insurance plans in the United States, including Medicare (with the exception of some supplemental plans), only cover patients domestically. When patients leave the country, they are without coverage. In the event of a medical emergency, obtaining treatment and hospital care in a foreign country can be very expensive. Medical “evacuations,” which may be required to get the traveler back home, can cost up to \$50,000 or more.

Typically, travel insurance costs between 5% and 7% of the total trip cost. Researching the different plans is important, as they can vary greatly. Get a printed copy detailing exactly which emergency medical treatment and/or medical evacuation and transport services are provided. Ask about coverage for preexisting medical conditions and about policy riders that will transport you back to the hospital of your choice as opposed to the nearest hospital of their choice, which may still be in a foreign country or in a city far from home.

More information on this and other related travel topics will soon be available on the Home Care NetWork Web page at www.chestnet.org/accp/networks.

Barbara Rogers, NetWork Member; and
Debra Karstadt, MA

Occupational and Environmental Health: Libby Asbestos and Beyond

Many physicians may consider “Libby asbestos” to be a problem limited to rural Montana and, as such, not germane to their practices. The ore (vermiculite) mined in Libby was initially milled in Libby and then transported to over 200 sites in the United States and Canada. The Environmental Protection Agency has estimated that 13 million US residents were exposed prior to 1990.

Once transported by rail, the vermiculite ore was “exfoliated” (otherwise known as expansion) by dropping the ore

through a vertical furnace with exposure to temperatures as high as 850°C. The expanded or “popped” vermiculite was then bagged and sold for insulation, packing material, or as a soil additive.

Vermiculite ore mined in Libby was contaminated with amphibole (tremolite) asbestos at concentrations of up to 25% or more (*Am Mineral*. 2003;88:1955 and Kelly et al. *Inhal Toxicol*. 2006;18[12]:941). As the ore was initially processed in Libby before shipment to the expansion plants, it is felt that the amphibole concentration in the processed ore (prior to expansion) was lower than that in the raw ore and that the shipped material contained amphibole asbestos in a concentration of 1% to 7% (US EPA Document 2000; 774-R-00-010). Kelly and colleagues (*Inhal Toxicol*. 2006;18[12]:941) described ambient air concentrations of 0.89 f/cc (1 h maximum) and personal air samples as high as 11.4 f/cc in a vermiculite expansion plant.

Similar to the experience in Wittenoon, Australia, and in the Italian asbestos cement industry, not only workers but also residents in proximity to the asbestos activity were exposed to amphibole fibers. Waste material was made available in dumps outside the processing plants, and children would play in the piles, with Kelly estimating that fiber exposure for the children was 1.4 f/cc. Kelly found contaminated housing sites up to 10 miles from the plant.

Horton and colleagues (*Inhal Toxicol*. 2008;20[8]:767) examined death certificates from 70 sites that received Libby ore; 11 of 70 sites showed an excess of mesothelioma mortality.

Rohs and colleagues (*Am J Respir Crit Care Med*. 2008;177[6]:630), in a 25-year follow-up study of 512 vermiculite expansion plant workers, found pleural changes in 28.7% and interstitial changes in 2.9%. While Rohs found the highest prevalence of pleural and interstitial disease in workers with the highest exposures, there are case reports of asbestosis following short-term exposure in an expansion plant worker (Wright et al. *Am J Respir Crit Care Med*. 2002;165[8]:1145) and in a worker whose only asbestos exposure was to finished vermiculite used in packing (Howard. *Am J Ind Med*. 2003;44[2]:214). Srebro and Roggli (*Am J Ind Med*. 1994;26[6]:809) also describe a 44-year-old man with biopsy-proven asbestosis from tremolite exposure, whose only known exposure was childhood residence near a vermiculite expansion plant.

Given the public health implications of millions environmentally exposed to fibers from vermiculite expansion plants, the Occupational and Environmental Health NetWork invites CHEST 2010 attendees to hear a special presentation by Dr Kelly Duncan—“Is Asbestos From Libby, Montana, More Toxic Than Other Types of Asbestos?”—on Sunday, October 31, at 11:15 AM.

Dr Richard Evans, FCCP
Steering Committee Member

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New Clinical Resources for Thromboses, Lung Cancer

Evidence-based clinical practice guidelines are important academic contributions but often are not easy to adapt to medical practice. In an effort to assist with the implementation of these guidelines, the ACCP has developed CD-ROM products based on the most recent editions of each of the core guidelines.

Antithrombotic Therapy, 8th ed.

The latest version of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines is the most evidence-based edition of these well-respected and much anticipated guidelines.

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These clinical resource tool kits can be ordered online at www.chestnet.org. Address questions to Sandra Zelman Lewis, PhD, at slewis@chestnet.org.

This Month in CHEST: Editor's Picks

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

- ▶ **Outcomes of Home-Based Diagnosis and Treatment of Obstructive Sleep Apnea.** By Dr R. P. Skomro, et al.
- ▶ **Small- and Moderate-Size Right-to-Left Shunts Identified by Saline Contrast Echocardiography Are Normal and Unrelated to Migraine**



Headache. By Dr T. D. Woods, et al.
▶ **Decrease in Long-term Survival for Hospitalized Patients With Community-Acquired Pneumonia.** By Dr J. Bordon, et al, and the CAPO Study Group.

RECENT ADVANCES IN CHEST MEDICINE

▶ **Lung Volume Reduction Therapies for Advanced Emphysema: An Update.** By Dr R. L. Berger, et al.

www.chestpubs.org

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The most recent *Journal Citation Report* shows that the Impact Factor of *CHEST* has risen to 6.36, more than a full point higher than last year's score of 5.15.

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Pulmonary Perspectives

Disparities in Health Care: Social Injustice and AMI

Beauchamp and Childress defined the major principles of bioethics: beneficence, maleficence, autonomy, and justice (Beauchamp and Childress. *Principles of Biomedical Ethics*, 5th ed. Oxford, UK: Oxford University Press; 2001). The principle of justice is cited least often. The counterpart of justice, social injustice, is relevant to disparities occurring in the United States, forming the basis for this discussion of health-care disparities observed in patients with acute myocardial infarction (AMI).

Two Institute of Medicine reports stated that health-care quality in the United States is below expectations (*To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press, 2000; *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press, 2001). The IOM drew attention to health care disparities experienced by rural US residents. Rural residents represent one in five citizens, are distributed throughout 87% of the US, are older, are more likely to have chronic illness, and generally exhibit poor health behaviors, including a reduced commitment to regular exercise (*Crossing the Quality Chasm*).

Many areas of the United States are not served by a hospital or are serviced by a regional critical access hospital. Critical access hospitals deliver fewer resources than urban facilities, receive less funding, lack staffing by emergency medicine physicians, and offer reduced, if any, access to cardiologists. In particular, disparities in treatment and mortality related to AMI have been documented, demonstrating that patients receiving care in urban areas have reduced mortality compared with those receiving care in rural communities.

The scope of social injustice related to rural health care negatively impacts mortality in AMI due to lack of adequately trained primary care physicians, reduced access to subspecialists, paucity of evidence-based medical guideline implementation, and distant locations of hospitals without trained EM specialists. This form of social injustice requires proactive and aggressive attention.

Representative Cases

At 4:00 AM, three patients awaken with "pressure-like" chest pain. Each has previously experienced chest discomfort and believed it to be heartburn, as prior episodes responded to antacid therapy. Each takes an antacid, repeats the

dose 10 min later, and fails to obtain relief for progressively worsening chest pain. Each summons help. In the interim, each individual develops diaphoresis and is unable to sit or stand due to dizziness.

Patient A is a stockbroker in Kansas City, MO. Paramedics arrive within 7 min; the patient's blood pressure is 80 systolic; an ECG is performed and interpreted by an EM physician. Within 3 min, oxygen, aspirin, and a beta-blocker are administered. The patient is taken to the closest hospital where an invasive cardiologist awaits. En route, he develops asystole, CPR is initiated, and he is emergently taken to the cardiac catheterization laboratory, where a temporary pacemaker is placed. He undergoes emergent angioplasty, thrombolytics are administered, and coronary artery stents are placed within 3 h of developing symptoms. He recovers overnight in the ICU and is released 5 days later with preserved cardiac function. During the hospitalization, he receives counseling about exercise and dietary modification, enrolls in a smoking cessation program, and is started on a regimen of a cholesterol-lowering medication, an angiotensin-converting enzyme (ACE) inhibitor, long-term beta-blocker therapy, and aspirin. He enters cardiac rehabilitation and is given an appointment to follow-up with a cardiologist in 1 week. He returns to work 4 weeks later.

Patient B is an unemployed construction worker living in a small Missouri town. An ambulance is called, arriving 30 min later. Paramedics place an IV, administer oxygen, record an ECG, administer a chewable aspirin, and transport him to the nearest hospital (50 beds, 20 miles away). The on-call primary care physician assesses the patient. Following blood tests and an ECG (60 min), Patient B is diagnosed with an AMI. A referral hospital is contacted, and the ECG and lab tests are faxed to the "on-call" cardiologist. Patient B has no health insurance, and two hospital administrators are contacted to accept the patient. Thrombolytic therapy is given after a pharmacist is paged from home to come to the hospital to prepare the medication.

After the thrombolytic therapy is administered, an ambulance transports the patient to a small landing strip outside of town, where a life-flight helicopter arrives soon afterwards.

En route to the referral hospital, Patient B develops an irregular heart rhythm, loses consciousness, and develops ventricular fibrillation. CPR is initiated, and defibrillation is performed until a cardiologist unsuccessfully attempts placement of a temporary pacemaker.

Editor's Insights

Chest physicians have many roles: medical education of patients and/or trainees; clinical practice; novel research and development of innovative therapies; and medical policy, planning, and medical specialty projections for the evolving needs of our constituents. All of these roles involve patient advocacy. Our ethical responsibilities to our patients are far more complex than those which we commonly recognize, such as decisions during end-of-life care. Though her illustrations

are hypothetical, the problem described is very real. Dr Willis has not only provided us with a discussion of a common and significant health-care disparity involving access to care and distribution of medical resources; she has also provided several potential remedies. Our concern in such matters is consistent with the long tradition of moral and humanitarian initiatives from the American College of Chest Physicians.

—Dr Marilyn G. Foreman, FCCP

The patient dies in the ED. An autopsy demonstrates evidence of an AMI.

Patient C lives in very rural Missouri area without EMS coverage. His son, who works 30 miles from home, is contacted and arrives 40 min later; he loads the patient into the back of a flatbed pickup truck and drives him to the closest facility, a 20-bed clinic/hospital located 1 h away. During transport, the patient loses consciousness, and upon arrival is pulseless. A family physician and a nursing assistant perform unsuccessful CPR. The patient dies 4 h after he developed symptoms. An autopsy demonstrates an AMI.

Each of these patients experienced a massive AMI. Patient A lived in a large metropolitan area and recovered without sequelae. Patient B lived in a small town and was first transported to a rural health facility and, subsequently, by helicopter, to a referral center. He died despite receiving thrombolytic therapy and transfer to a referral center as quickly as possible. Patient C lived in a very remote rural area and received no intervention from the time of awakening with chest pain until arriving at the closest hospital.

Same diagnosis, three different outcomes, with only one of three patients with preserved life. These cases are evidence of an all too common but somewhat well-kept secret in the United States: a critical lack of access to state-of-the-art medical care in rural America. This represents social injustice.

"Justice," said Aristotle, "involves treating like cases alike and different cases differently" (*Medicine and Social Justice*. Oxford, UK: Oxford University Press, 2002). Patients A, B, and C did not receive equitable treatment. In the late 1990s, there were 134.1 specialists per 100,000 residents in urban counties in the United States, compared with 40.1 per 100,000 in rural counties (Rosenblatt RA and Hart LG. "Physicians and rural America." In: Ricketts TC, ed. *Rural*

Health in the United States. Oxford, UK: Oxford University Press, 1999; 38-51). Despite the presence of evidence-based medicine protocols for treatment of AMI, rural centers are generally less efficient in making a prompt diagnosis and less likely overall to implement evidence-based guideline therapy.

A study published in 2002 evaluating care for AMI among Medicare patients found that these patients treated in rural hospitals were less likely than urban patients to receive aspirin during hospitalization or at discharge, IV nitroglycerin, heparin, and either thrombolytics or percutaneous transluminal coronary angioplasty (Baldwin et al. *Quality of Care for Acute Myocardial Infarction in Rural and Urban US Hospitals*. Working Paper #72. Seattle, WA: WWAMI Rural Health Research Center, University of Washington; June 2002).

Though the existence of health-care disparities related to access has been acknowledged, effective and meaningful long-term action plans have not yet been instituted. Some suggest that changes are required, beginning with undergraduate medical education (Rabinowitz et al. *Acad Medicine*. 2008;83[3]:235; Glass et al. *Acad Medicine*. 2008;83[10]:952).

Procuring the right mix of specialty and primary care providers for rural areas will be critically important in addressing rural health-care disparities. Linking rural hospitals and health clinics with tertiary care hospitals via distance technology/telemedicine systems offers promise. One mechanism that has shown some success is the concept of an e-ICU, which has been shown in preliminary studies to reduce mortality in small rural centers. Widespread implementation of e-ICU services in rural centers has the potential to positively impact diagnostic capabilities and implementation of evidence-based protocols, as well as appropriately timed, scoop-and-run transfers to referral centers.

Continued on following page

Dr Marilyn G. Foreman, FCCP
Editor, *Pulmonary Perspectives*

Dr Loren J. Harris, FCCP
Deputy Editor, *Pulmonary Perspectives*

Continued from previous page

Conclusion

In order to achieve social justice in rural health care, increased access to quality health care by rural residents must be provided. This represents a challenge, particularly in today's economic and political climate.

Only with increased numbers of appropriately trained primary care providers practicing evidence-based medicine, linked with a network of subspecialist providers, will substantive changes in outcomes begin to occur in rural America.

Rural residents, who account for more than one in five of all US citizens, deserve social justice and access to state-of-the-art health care. Anything less represents social injustice.

Critical care physicians must join together to highlight the injustices experienced by many of the rural residents of our country. Absent such efforts, the health-care community is passively allowing social injustice to continue. ■

Dr Sandra K. Willsie, MA, FCCP
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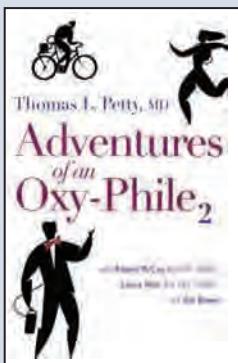
August Lessons

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A Personal Recommendation: Top 5 Vancouver Restaurants

Enjoying a nice meal in Vancouver with family, friends, or colleagues can be the perfect way to experience the city. Need some recommendations? Meet Dr Mark FitzGerald, a Professor of Medicine, University of British Columbia, and Director, Centre for Lung Health, Vancouver, BC, Canada. This Vancouver resident says, "I'm lucky and live in the best place in the world." Check out some of his favorite Vancouver restaurants.

► **Le Crocodile.** This is a great French restaurant—never a disappointing meal. \$\$\$\$ <http://lecrocodilerestaurant.com>

► **Bishop's.** Great Northwestern cuisine is served in a very relaxed and attentive manner. \$\$\$\$ www.bishopsonline.com

► **La Régalade.** This is a typical French bistro, only much better than in Paris. La Régalade is on the North Shore but a great place to stop on the way back



DR MARK FITZGERALD

from a North Shore hike. Reservations are essential. \$\$\$ www.laregalade.com

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FCCPs in the News Near and Far

Dr Steven E. Weinberger, FCCP, FACP, has been appointed Executive Vice President and Chief Executive Officer of the American College of Physicians. The selection was made based on a national search and recommendations from a search committee appointed by the ACP Board of Regents. An experienced administrator and board-certified

internist and pulmonologist, Dr Weinberger has served as the ACP Deputy Executive Vice President since 2009 and as the ACP's Senior Vice President for Medical Education and Publishing since 2004. Prior to joining the ACP, Dr Weinberger served as faculty associate dean for medical education and professor of medicine at Harvard Medical School. ■

Dr Silvia Quadrelli, FCCP, was recently awarded the Bicentennial Medal from the City of Buenos Aires "in recognition of her lifetime achievements and generous contributions to today's society." This is one of Argentina's most prestigious honors.

Dr Quadrelli graduated from the University of Buenos Aires in 1979. She holds a degree in Medical Ethics from the Faculty of Social Sciences, a Master's degree in education, and is completing her Doctorate in Philosophy. She has been an international leader in humanitarian efforts, working with Doctors Without Borders and Doctors of the World from 1982 to 2007.

Overall she has participated in more than 40 international humanitarian aid missions, including leading many large-scale efforts in Kosovo, El Salvador, Argentina, Iraq, Yemen, Sri Lanka, and many other countries.

In addition to her history of holding many leadership positions in national and South American respiratory societies, she is a prior recipient of a CHEST Foundation Governor's Community Service Award, a Fellow of the American College of Chest Physicians, a member of the ACCP Cultural Diversity NetWork, and a current ACCP Governor for Argentina. ■

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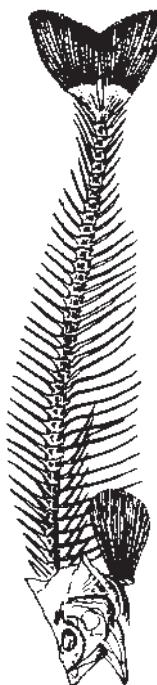
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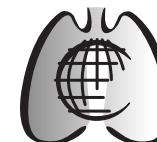
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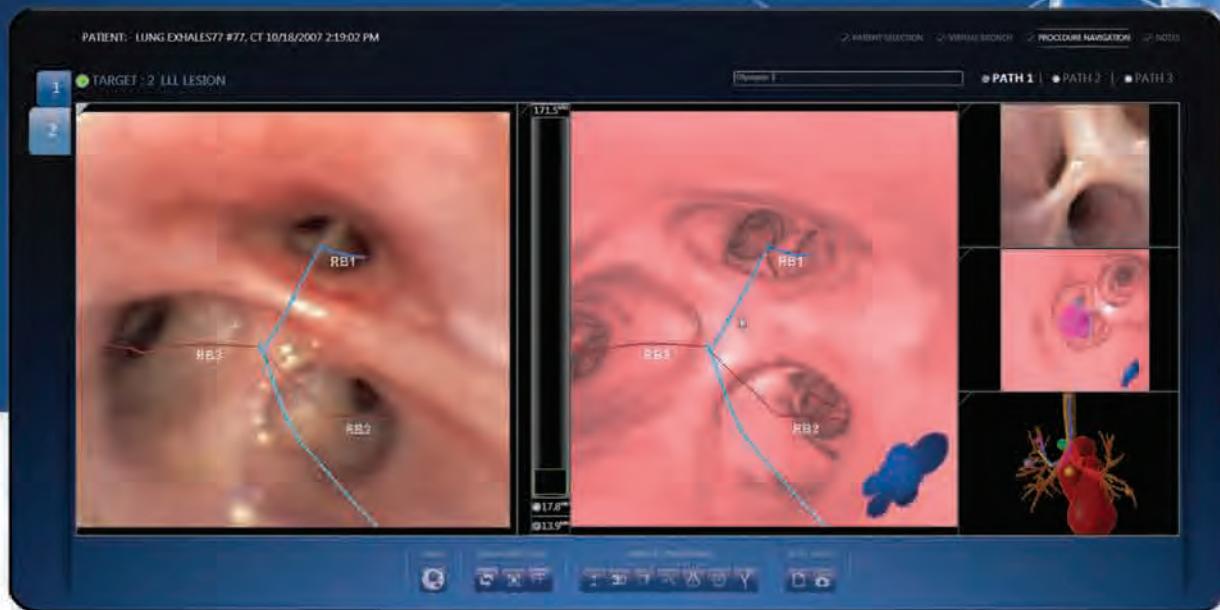
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