VOL. 2 • NO. 9 • SEPTEMBER 2007

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

UNIVERSITY OF MICHIGAN HEALTH SYSTEM

The Biolung prototype will serve just as a bridge to transplantation, not as a permanent device, explained Dr. Robert Bartlett.

Artificial Lung Moves Closer to Reality

BY DOUG BRUNK
Elsevier Global Medical News

Human clinical trials of an implantable artifical lung that can serve as a bridge to lung transplantation may be just 3-4 years away.

In August, the National Institutes of Health awarded a $5 million, 5-year grant to a team of researchers, led by Dr. Robert Bartlett, to refine the device for use in patients. The device, known as the Biolung, has thus far been tested in sheep.

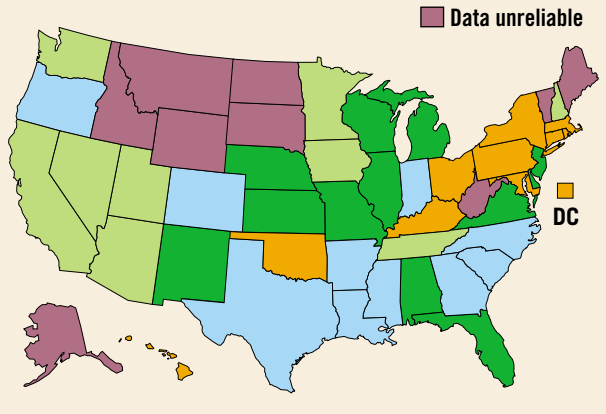
"When lay people hear about this, they think about a permanent device like an artificial heart," said Dr. Bartlett, professor emeritus of surgery at the University of Michigan, Ann Arbor, and a pioneer in the development of artificial organs. "But clearly that won't be practical, at least in the foreseeable future. It will be just a bridge to transplantation. It will come along in the usual fashion of artifical organs: relatively slowly."

In the 1980s, Dr. Bartlett led the researchers who developed the extracorporeal circulation membrane oxygenation (ECMO) machine, which is used worldwide to circulate and oxygenate the blood of patients with acute lung failure. ECMO can be used safely for weeks while a patient is bedridden in the intensive care unit, but the typical wait for a lung transplant is many months. The purpose of the Biolung device is to help lung transplant

See **Lung** • *page 4*

VITAL SIGNS

Asthma Prevalence in Children Aged 0-17 Years



Note: Based on the annual average for 2001-2005.
Source: Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS

NAEPP's Asthma Guidelines Undergo Sweeping Update

Comprehensive changes to four key areas.

BY SHARON WORCESTER
Elsevier Global Medical News

A panel of U.S. asthma experts hopes the first major overhaul of asthma diagnosis and management guidelines in a decade will leave more patients breathing easier.

An emphasis on prevention of exacerbations via asthma control is the key change in the newly updated guidelines, which were released by the National Asthma Education and Prevention Program (NAEPP), a program coordinated by the National Heart, Lung, and Blood Institute of the National Institutes of Health.

In particular, the panel called for increased emphasis on selecting treatment based on a patient's needs and level of asthma control, and it separated this control into two interlinked domains: one focusing on current impairment, and one on future risk.

"The goal of asthma therapy is to control asthma so that patients can live active, full lives while minimizing their risk of asthma exacerbations and other problems," explained panel chairman Dr. William W. Busse, of the department of medicine at the University of Wisconsin, Madison.

Proper asthma control depends on both current impairment and future risk, Dr. Busse said during a teleconference on the guidelines.

Incorporating the latest in asthma research findings, the panel expanded four key components of asthma care outlined in the original guidelines, which were introduced in 1991 and updated in 1997. Those components include assessment and monitoring, patient education, control of environmental factors and other conditions that can affect asthma, and medications.

"Overall, these components have stood the test of time, and many of the earlier

See **Update** • *page 5*

INSIDE

Medicare: No Pay for 'Preventable' Errors

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

In a continuing effort to link payments to quality, Medicare will soon stop paying hospitals for certain conditions and infections acquired after admission.

The change was mandated by Congress under the Deficit Reduction Act and will go into effect in October 2008. Starting this October, hospitals will be required to report on secondary diagnoses that are present at the time of admission.

Officials at the Centers for Medicare and Medicaid Services have identified eight "reasonably preventable" events that can be avoided in most cases by engaging in good medical practice. Hospitals will not receive additional payments for these secondary diagnoses if they develop after admission: an object left in the patient during surgery; air embolism; blood incompatibility; catheter-associated urinary tract infections; pressure ulcers; vascular catheter–associated infections; mediastinitis after coronary artery bypass graft surgery; and falls.

CMS officials will consider adding three other hospital-acquired conditions next year: ventilator-associated pneumonia; *Staphylococcus aureus* septicemia; and deep vein thrombosis/pulmonary embolism.

Under the new policy, the costs cannot be passed along to patients. However, hospitals will not bear the total financial risk of these cases because the payment policy will not affect

See **No Pay** • *page 5*

CHEST PHYSICIAN
60 Columbia Rd., Bldg. B
Morristown, NJ 07960
CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

Lupus Induced by Biologics: 'It Happens, but It's Rare'

BY NANCY WALSH
Elsevier Global Medical News

BARCELONA — Cases of drug-induced lupus have been reported in patients who were treated with anti–tumor necrosis factor agents, Dr. Manuel Ramos-Casals said at the annual European Congress of Rheumatology.

"As these drugs are being used in an expanding number of diseases, there has been a corresponding increase in the number of reports of the development of autoimmune processes, including lupus, vasculitis, and interstitial lung diseases," said Dr. Ramos-Casals of the department of autoimmune diseases, Hospital Clinic, Barcelona.

As of December 2006, Medline searches identified 92 cases of patients being treated with biologic drugs who developed a lupus-like syndrome after a mean 41 weeks of therapy, he said.

Of these patients, 77 (84%) were female and 15 (16%) were male, with a mean age of 51 years at the development of lupus features.

A total of 77 were receiving the drugs for rheumatoid arthritis, eight for Crohn's disease, and seven for other rheumatic diseases.

The anti–tumor necrosis factor (anti-TNF) agents involved were infliximab in 40 patients (44%), etanercept in 37 (40%), and adalimumab in 15 (16%).

Lupus features included the presence of antinuclear antibodies and anti–double-stranded DNA antibodies in 86 cases (94%), cutaneous manifestations in 82 (89%), musculoskeletal features in 36 (39%), and general manifestations such as fever, malaise, and asthenia in 27 (29%).

Only 32 patients (35%) fulfilled the full criteria for systemic lupus erythematosus, however.

Cutaneous features were more common among patients who were receiving etanercept than among those receiving infliximab (44% compared with 12%), while serositis was more common among patients receiving infliximab (24% compared with 3%). "There may be differences in the expression of lupus features according to the anti-TNF drug used," he said.

The anti-TNF drug was withdrawn in 86 (94%) of cases, and treatment of the syndrome included corticosteroids in 37 (40%) and immunosuppressive agents in 11 (12%).

All but one of the patients improved, and there were no deaths.

Dr. David A. Isenberg of the Centre for Rheumatology, University College, London, noted that it was important to consider the frequency of these events.

"The British Society for Rheumatology biologics registry now includes 11,000 patients, 4,000 each on infliximab and etanercept and 3,000 on adalimumab. In 5 years we have seen only four to six cases of drug-induced lupus, for a frequency of 0.1%-0.5%. It happens, but it's rare," Dr. Isenberg said. ■

CAP Outcomes No Worse When HIV Is Present

SAN FRANCISCO — Patients with HIV do just as well as patients without the virus when faced with bacterial community-acquired pneumonia, according to a poster presentation by Dr. Maricar Malinis at the International Conference of the American Thoracic Society.

Dr. Malinis, of the University of Louisville (Ky.), and colleagues concluded that "the decision to hospitalize a patient [with community-acquired pneumonia] should not be based on the HIV status, but rather on the severity of illness."

The investigators conducted a large, retrospective study based on a database maintained by the Community-Acquired Pneumonia Organization (CAPO). A total of 2,908 patients were included in the analysis, of whom 118 (4.1%) were HIV positive.

There were no significant differences between the groups in all-cause mortality or mortality related to community-acquired pneumonia, measured at hospital discharge.

Dr. Malinis and her co-investigators wrote that the results of the study suggest that, at least in the area of hospitalization, the current national guidelines for managing patients with community-acquired pneumonia can be applied to patients who have HIV.

—Robert Finn

Printers, Nurses at Higher Risk of Occupational Asthma

Exposure to substances in the workplace causes more than 10% of all cases of adult-onset asthma, according to an international prospective population-based survey published in the July 28 issue of the Lancet.

The occurrence of occupational asthma is about 250-300 cases/million people, much higher than the 20-30 cases/million people seen in previous studies in France, the United Kingdom., and the United States, investigators said.

The highest increased risk of occupational asthma was seen in printing, woodworking, and nursing, wrote the researchers, led by Dr. Manolis Kogevinas of the Center for Research in Environmental Epidemiology of the Municipal Institute of Medical Research in Barcelona.

They studied 6,837 participants, aged 20-44, who had taken part in the European Community Respiratory Health Survey from 1990 to 1995. These participants did not report respiratory symptoms or a history of asthma. They were followed for a mean of 9 years and completed a follow-up survey between 1998 and 2003 (Lancet 2007;370:336-41).

The researchers obtained occupational histories from the participants, asking if they had 1 of 13 types of high-risk jobs—including baking, painting, chemical industry positions, nursing, hairdressing, and cleaning; if they had jobs with a risk of exposure to irritants linked to occupational asthma; and if they had been exposed to inhalation accidents. All measurements were adjusted for age, sex, smoking status, and research site.

Participants were at higher risk of having had an asthma attack or had used asthma drugs in the 12 months before the follow-up survey if they worked in a high-risk occupation, compared with participants who worked in professional, clerical, or administrative jobs (relative risk 1.69).

Those in high-risk occupations also were at increased risk (RR = 1.58) of occupational asthma if their job involved exposure to one of several high-risk substances, including latex, flour, industrial chemicals, and bioaerosols. The risk of occupational asthma was greatest in printing (RR = 2.37), woodworking (RR = 2.22), and nursing, RR = 2.22).

—Jonathan Gardner

QUIT RATES SUPERIOR TO ZYBAN® AT 12 WEEKS IN 2 HEAD-TO-HEAD CLINICAL TRIALS (*P*=.0001)[1,2]*

44% of subjects who received CHANTIX 1 mg bid quit smoking by the end of 12 weeks vs:

- Approximately 30% of subjects who received Zyban 150 mg bid
- Approximately 17.5% of subjects who received placebo

WELL-STUDIED TOLERABILITY AND SAFETY PROFILE

- The most common adverse reactions included nausea, sleep disturbance, constipation, flatulence, and vomiting. Nausea occurred in 30% of subjects while 3% discontinued due to nausea

CONVENIENT *PAK* DOSING

- *PAK*s are designed to simplify prescribing and to help improve patient adherence

GET QUIT™ **SUPPORT PLAN**

- A personalized behavioral support program designed to address critical behavioral components of smoking cessation, such as relapse

Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.

Dosage adjustment with CHANTIX is recommended in patients with severe renal impairment or in patients undergoing hemodialysis.

Smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, such as theophylline, warfarin, and insulin. Dosage adjustment for these drugs may be necessary.

CHANTIX™ (varenicline) TABLETS

TURN MORE SMOKERS INTO QUITTERS

*Results from 2 identically designed, 52-week (12 weeks pharmacotherapy, 40 weeks nonpharmacotherapy follow-up), randomized, double-blind, parallel-group, multicenter clinical trials (study 4: N=1022; study 5: N=1023) in which CHANTIX 1 mg bid was compared with Zyban 150 mg bid and placebo for efficacy and safety in smoking cessation. For trial inclusion, subjects must have smoked at least 10 cigarettes per day over the past year, with no period of abstinence greater than 3 months, and must have been bupropion naive. The primary efficacy end point in both trials was the carbon monoxide (CO)–confirmed 4-week continuous abstinence rate for weeks 9 through 12, defined as the percentage of subjects who reported no smoking (not even a puff) or use of any nicotine-containing products confirmed by an exhaled CO measurement of 10 ppm or less at each clinic visit. (Studies 4 and 5 from the CHANTIX package insert.)[1,3-5]

Subjects were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each clinic visit in accordance with Agency for Healthcare Research and Quality guidelines.[5]

Device May Increase Transplants

Lung • *from page 1*

candidates stay alive and mobile while they wait for a donor lung.

The Biolung prototype Dr. Bartlett is studying uses tiny hollow fibers and the heart's own pumping power to oxygenate blood. The device is made of plastic, weighs about 2 pounds, and is about the size of a soda pop can. It is connected to the pulmonary artery and is strapped in with a vest outside the chest wall. The device weighs 7-8 pounds when it's full of blood.

"The device will be outside [the chest wall] because we expect to have to change it from time to time. This makes it easy to change, rather than having to do a new operation every time we change it," Dr. Bartlett said.

The Biolung prototypes are being made by MC3 Inc., a bioengineering firm in Ann Arbor that Dr. Bartlett cofounded 15 years ago with two bioengineers.

Investigators at the University of Maryland, Baltimore; the University of Kentucky, Lexington; and the University of Pittsburgh in the United States, and in Osaka, Japan, are working on Biolung prototypes.

At the University of Kentucky, Dr. Joseph Zwischenberger, FCCP, and his associates are studying a version of the Biolung that is intended to tolerate right heart failure. The modification contains a pump about the size of a 35-mm film cartridge.

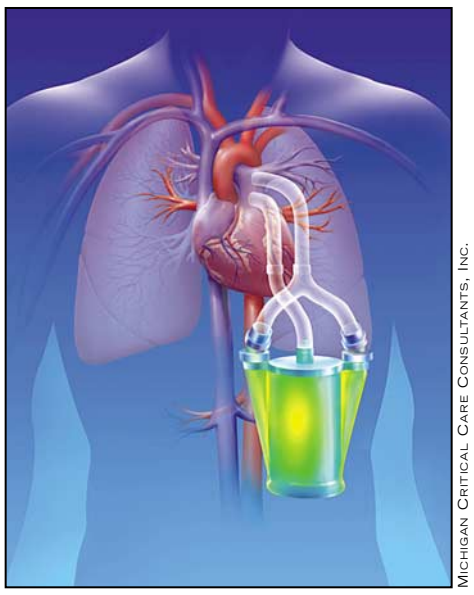
"In humans [with lung failure], as much as half the time the heart's also in some degree of failure, because the lungs and the heart are connected in series and are dependent on each other," explained Dr. Zwischenberger, chair of the department of surgery at the University of Kentucky.

"When the lungs fail, often the heart will fail. So before going to clinical trials, I felt it was very important to have a version of this device that could support right heart failure," he added.

The pump is designed to accomplish the pumping requirements of the right ventricle, until the lung recovers or is replaced by a transplant.

Dr. Zwischenberger likened the development of the artifical lung to the development of the artificial heart.

It took 2 decades for an artificial heart to be implanted in a human. "Learning from that experience, I feel very strongly that the [Food and Drug Administration] is going to allow us to first use [an artificial lung] device that is paracorporeal—partly to improve safety, partly to allow ready access to this developing technology, and partly to allow immediate large-animal testing to continue device improvement," he said.



MICHIGAN CRITICAL CARE CONSULTANTS, INC.

The Biolung uses tiny hollow fibers and the heart's own pumping power.

To date, the Biolung has been used successfully in sheep for 30 days. Dr. Zwischenberger believes that if researchers can ensure consistent performance for a month or two in large prospective studies of sheep, they can then do a pilot study in humans.

Dr. Bartlett predicted that the Biolung will help expand the pool of transplantable lungs. For example, he said, organ donors who have experienced severe brain damage usually have some degree of lung failure, such as aspiration or pneumonia, and are not considered lung donors. But the Biolung could make a slightly damaged donor lung acceptable for transplant. "It could allow that transplanted lung [time] to heal," he said.

About 1,000 lung transplantations are performed in the United States each year. "The results are quite good," Dr. Bartlett said. "The limiting factor is donors. It's estimated that there are about 20,000 patients each year who are potential lung transplant recipients."

Ideal candidates for the Biolung will be patients with primary pulmonary hypertension and pulmonary fibrosis. "Most of the emphysema patients and the cystic fibrosis patients do best if you transplant both lungs rather than leave one bad one," he said. "So they're one step more complicated in terms of getting appropriate donors."

CHANTIX™ (varenicline) TABLETS

Pfizer

Before prescribing, please consult Full Prescribing Information.

INDICATIONS AND USAGE
CHANTIX is indicated as an aid to smoking cessation treatment.

PRECAUTIONS

General Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

Effect of smoking cessation: Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

Drug Interactions Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions (See **Full Prescribing Information, CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis. Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis. Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of fertility. There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

Pregnancy Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). **Nonteratogenic effects** Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Labor and delivery** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSAGE AND ADMINISTRATION, Special Populations**).

Information for Patients:
- Patients should be instructed to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date.
- Patients should be advised that CHANTIX should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening.
- Patients should be advised that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should be informed that nausea and insomnia are side effects of CHANTIX and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with CHANTIX.
- Patients should be advised to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them.

ADVERSE REACTIONS
During the premarketing development of CHANTIX, over 4500 individuals were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less. In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg BID was 12% for CHANTIX compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates for the most common adverse events in CHANTIX treated patients were as follows: nausea (3% vs. 0.5% for placebo), headache (0.6% vs. 0.9% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo). Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

The most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting. Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

The most common adverse event associated with CHANTIX treatment is nausea. For patients treated to the maximum recommended dose of 1 mg BID following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

Table 3 shows the adverse events for CHANTIX and placebo in the 12 week fixed dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5). MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg BID dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1mg BID N=821	Placebo N=805
GASTROINTESTINAL			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain*	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4

(Table 3 continued)

PSYCHIATRIC DISORDERS			
Sleep Disorders/Disturbances			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/THORACIC/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnoea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3, though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with CHANTIX 1 mg BID in a one-year study, compared to 8% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS**. ***Infrequent***: Anemia, Lymphadenopathy. ***Rare***: Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS**. ***Infrequent***: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. ***Rare***: Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **EAR AND LABYRINTH DISORDERS**. ***Infrequent***: Tinnitus, Vertigo. ***Rare***: Deafness, Meniere's disease. **ENDOCRINE DISORDERS**. ***Infrequent***: Thyroid gland disorders. **EYE DISORDERS**. ***Infrequent***:: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. ***Rare***: Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS** ***Frequent***: Diarrhea, Gingivitis. ***Infrequent***:: Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. ***Rare***: Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS**. ***Frequent***: Chest pain, Influenza like illness, Edema, Thirst. ***Infrequent***:: Chest discomfort, Chills, Pyrexia. **HEPATOBILIARY DISORDERS**. ***Infrequent***:: Gall bladder disorder. **IMMUNE SYSTEM DISORDERS**. ***Infrequent***:: Hypersensitivity. ***Rare***: Drug hypersensitivity. **INVESTIGATIONS**. ***Frequent***: Liver function test abnormal, Weight increased. ***Infrequent***:: Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal. **METABOLISM AND NUTRITION DISORDERS**. ***Infrequent***:: Diabetes mellitus, Hyperlipidemia, Hypokalemia. ***Rare***: Hyperkalemia, Hypoglycemia. **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS**. ***Frequent***: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. ***Infrequent***:: Arthritis, Osteoporosis. ***Rare***: Myositis. **NERVOUS SYSTEM DISORDERS**. ***Frequent***: Disturbance in attention, Dizziness, Sensory disturbance. ***Infrequent***:: Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. ***Rare***: Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **PSYCHIATRIC DISORDERS**. ***Frequent***: Anxiety, Depression, Emotional disorder, Irritability, Restlessness. ***Infrequent***:: Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. ***Rare***: Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS**. ***Frequent***: Polyuria. ***Infrequent***: Nephrolithiasis, Nocturia, Urine abnormality, Urethral syndrome. ***Rare***: Renal failure acute, Urinary retention. **REPRODUCTIVE SYSTEM AND BREAST DISORDERS**. ***Frequent***: Menstrual disorder. ***Infrequent***: Erectile dysfunction. ***Rare***: Sexual dysfunction. **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS**. ***Frequent***: Epistaxis, Respiratory disorders. ***Infrequent***:: Asthma. ***Rare***: Pleurisy, Pulmonary embolism. **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** ***Frequent***: Hyperhidrosis. ***Infrequent***: Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. ***Rare***: Photosensitivity reaction. **VASCULAR DISORDERS**. ***Frequent***: Hot flush, Hypertension. ***Infrequent***: Hypotension, Peripheral ischemia, Thrombosis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Varenicline is not a controlled substance. Humans: Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction. In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers. Animals: Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

OVERDOSAGE

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see **Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Patient Populations**), however, there is no experience in dialysis following overdose.

DOSAGE AND ADMINISTRATION

Usual Dosage for Adults Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt. The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date. CHANTIX should be taken after eating and with a full glass of water. The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1–3:	0.5 mg once daily
Days 4–7:	0.5 mg twice daily
Days 8–End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently. Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence. Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Special Populations

Patients with impaired renal function No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with End-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See **Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal impairment**).

Dosing in elderly patients and patients with impaired hepatic function No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See **PRECAUTIONS, Geriatric Use**).

Use in children Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Rx only May 2007, Version 2.0

CHU00217 © 2007 Pfizer Inc. All rights reserved. Printed in USA/August 2007 Pfizer U.S. Pharmaceuticals

Panel Revises Asthma Guidelines

Update • *from page 1*

recommendations have been solidly confirmed by additional research throughout the years," Dr. Busse noted in a statement released by the NAEPP.

Inhaled corticosteroids, for example, remain the best long-term control treatment for asthma patients of all ages, the panel said. However, new information and developments were substantial enough to warrant the update, he said.

Changes to the four components of asthma care include:

▶ **Assessment and monitoring.** Key additions to the assessment and monitoring component of the guidelines include the use of multiple measures to assess patient impairment, such as frequency and intensity of symptoms, lung function, and effects on daily activities. In particular, the guidelines stress that although patients may experience few day-to-day effects of asthma, they may still be at risk for exacerbations due to seasonal effects (such as a peak in viral infections in the fall).

▶ **Patient education.** The updated guidelines call for increased efforts to teach patients self-monitoring skills and asthma management—including the use of a written asthma action plan that includes instructions for daily treatment and methods for handling symptoms that may arise. Other recommendations include improved communication with patients and families, as well as the expansion of educational opportunities in settings such as schools and community centers.

▶ **Control of environmental factors.** The panel added new evidence supporting a variety of approaches to limit exposure to allergens and other substances that can worsen asthma. The revisions call for the use of multiple approaches rather than single steps, which are rarely sufficient.

▶ **Medications.** The guidelines now recommend a stepwise approach, in which medication doses or types are stepped up or down as needed, based on an individual's level of asthma control.

Another important new factor in the updated guidelines is increased stratification by age group. Previously, patients were divided into two age groups: 0-5 years and older than 5 years. The updated version divides patients into 0-4 years, 5-11 years, and older than 11 years to account for differences in developmental stages and greater understanding about how medications work in each age group.

The NAEPP appointed a new panel to develop an action plan for improving implementation of guidelines. A report on implementation is expected to be released in October. ■

Dr. Jay Peters, FCCP, Vice-Chair, ACCP Airways Disorders NetWork, comments: *The new NIH guidelines are the first comprehensive update in almost a decade and should prove very useful to clinicians. They shift the focus from the level of asthma severity to the level of asthma control, with the hope that optimizing asthma therapy will lead to patients living a full and active life with few or no exacerbations. New data about risk and benefits of asthma therapy are reviewed, and new scientific data about risk factors (like obesity) and tools for monitoring asthma are discussed.*

IN THIS ISSUE

CHEST PHYSICIAN Is Online

CHEST PHYSICIAN is available on the Web at www.chestnet.org/about/publications.

Error Policy Gives Pause to Some

No Pay • *from page 1*

Medicare's high-cost outlier policy. CMS will continue to use the hospital's total charges for all inpatient services provided during a patient's stay when determining whether the case qualifies for an outlier payment.

The policy was issued as part of the Medicare acute care hospital inpatient prospective payment system final rule, which was published in the Federal Register on Aug. 22.

The move was applauded by payers and quality advocates, but hospitals and physicians raised some red flags about the change.

In a June 12 letter to CMS, the American Medical Association voiced concerns that the policy could have "significant unintended consequences for patients."

"The concept of not paying for complications that are often a biological inevitability regardless of safe practice is discriminatory and could be punitive to those patients at the greatest risk," wrote Dr. Michael D. Maves, executive vice president and CEO of the AMA. "Certain patients, including those who are older, have medical comorbidities, or have otherwise compromised immune systems, are more susceptible to infection and other complications."

Although the CMS focus on quality and patient safety is laudable, agency officials are overreaching with their list of conditions, said Dr. Junaid Khan, a cardiothoracic surgeon in Oakland, Calif.

For example, surgical site infections are a significant problem, but it's unlikely that they can be eliminated even with proper adherence to guidelines, he said, adding that a more global approach would be more useful at identifying systems issues and improving patient safety.

The devil is likely to be in the details, said Dr. Jeffrey Milliken, FCCP, a cardiothoracic surgeon at the University of California, Irvine. The nature of the underlying disease and whether clinical guidelines were followed must be considered in order for the policy to be fair and effective.

The American Hospital Association supports the inclusion of only three of the conditions outlined by CMS (an object left in during surgery, air embolism, and blood incompatibility). However, there are concerns about whether the other conditions are always or even usually preventable, even with excellent care, said David Allen, an AHA spokesman.

But the Medicare policy shift was welcomed by health plans and some quality advocates.

The announcement by CMS is consistent with the move to pay for quality, said Susan Pisano, a spokesperson for America's Health Insurance Plans. The new policy provides an incentive for hospitals to develop processes to avoid these conditions, she said.

Officials at the National Committee for Quality Assurance (NCQA) also favor the policy change. "If we can't say no to the wrong kinds of care, it going to be virtually impossible to say yes to the right kinds," said Jeff Van Ness, a spokesman for NCQA.

The CMS policy sends a "loud and clear signal" to hospitals that they must pay attention to these preventable events, said Rachel Weissburg, a program associate at the Leapfrog Group, a coalition of employers focused on health care quality and transparency.

In fact, officials at the Leapfrog Group would like to see CMS expand the list of hospital-acquired conditions to include the 28 serious reportable events—rare medical errors that should never happen to a patient—that have been compiled by the National Quality Forum.

The Leapfrog Group launched a project last year to encourage hospitals to develop plans to avoid these serious reportable events. ■

AMERICAN COLLEGE OF CHEST PHYSICIANS®

AMERICAN COLLEGE OF CHEST PHYSICIANS

Editor in Chief Susan M. Harding, M.D., FCCP
President Mark J. Rosen, M.D., FCCP
Executive Vice President and CEO Alvin Lever, MA, FCCP (Hon)
Vice President, Publications Stephen J. Welch
Assistant Vice President, Editorial Resources Pamela L. Goorsky
Medical Copy Editor Peggy Eastmond, RD
Editorial Assistant Arren M. Graf

EDITORIAL ADVISORY BOARD

Doreen Addrizzo-Harris, M.D., FCCP, New York
Robert J. Cerfolio, M.D., FCCP, Alabama
Vera A. De Palo, M.D., FCCP, Rhode Island
Stephen A. Geraci, M.D., FCCP, Mississippi
LeRoy M. Graham, M.D., FCCP, Georgia
Jeffrey W. Hawkins, M.D., FCCP, Alabama
Peter McKeown, M.B.B.S., FCCP, North Carolina
Stephen M. Pastores, M.D., FCCP, New York
Aymarah M. Robles, M.D., FCCP, Florida
Paul A. Selecky, M.D., FCCP, California
Gerard A. Silvestri, M.D., FCCP, South Carolina
Keith M. Wille, M.D., FCCP, Alabama

E-mail: chestphysiciannews@chestnet.org

CHEST PHYSICIAN

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

The statements and opinions expressed in **CHEST PHYSICIAN** do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Elsevier Society News Group, a division of Elsevier Inc., do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

Address Changes: Fax changes of address (with old mailing label) to 973-290-8245.

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

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

©Copyright 2007, by the American College of Chest Physicians

ELSEVIER SOCIETY NEWS GROUP, A DIVISION OF INTERNATIONAL MEDICAL NEWS GROUP

President, IMNG Alan J. Imhoff
Director, ESNG Mark Branca
Executive Director, Editorial Mary Jo M. Dales
Executive Editor, IMNG Denise Fulton
Executive Editor, EGMN Kathy Scarbeck
Publication Editor Terry Rudd
Publication Associate Editor Jay C. Cherniak
VP, Medical Education Sylvia H. Reitman
Senior Director, Marketing and Research Janice Theobald
Circulation Analyst Barbara Cavallaro
Executive Director, Operations Jim Chicca
Director, Production and Manufacturing Yvonne Evans
Production Manager Judi Sheffer
Art Director Louise A. Koenig
Display Advertising Manager The Walchli Tauber Group: 443-512-8899, fax 443-512-8909, gary.walchli@wt-group.com, stephen.tauber@wt-group.com
Classified Sales Manager Rhonda Beamer, 443-512-8899, fax 443-512-8909, rhonda.beamer@wt-group.com
ADVERTISING OFFICES 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250
CLASSIFIED ADVERTISING OFFICES The Walchli Tauber Group, 2225 Old Emmorton Rd., Suite 201, Bel Air, MD 21015, 443-512-8899
EDITORIAL OFFICES 5635 Fishers Lane, Suite 6000, Rockville, MD 20852, 240-221-4500, fax 240-221-2541

Gene Mutations Predicted Response to Erlotinib, Gefitinib

Screening tests can help select NSCLC patients who are likely to benefit from tyrosine kinase inhibitors.

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

CHICAGO — Two prospective studies suggest that clinicians will be able to improve survival in non–small cell lung cancer by selecting patients with specific mutations that respond to erlotinib and gefitinib for treatment with those agents.

The approach is feasible, according to results of the first prospective, multicenter, phase II trial to attempt it in the United States. Based on the presence of epidermal growth factor receptor (EGF-R) mutations in tumor samples, Dr. Lecia V. Sequist and her colleagues gave gefitinib (Iressa) to 31 patients as a first-line treatment for advanced non–small cell lung cancer (NSCLC). She reported overall survival as 73% at 1 year.

A second prospective study, conducted by the Spanish Lung Cancer Group, reported that the presence of EGF-R mutations on exons 19 or 21 in serum samples was associated with poorer performance status in advanced NSCLC patients and with variations in responses to erlotinib. Dr. Teresa Morán reported finding mutations in nearly 100% of performance status 2 patients with clinical characteristics suggestive of EGF-R mutations.

Dr. Sequist of Massachusetts General Hospital, Boston, and Dr. Morán of the Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Barcelona, presented the studies at the annual meeting of the American Society of Clinical Oncology. The U.S. study received support from AstraZeneca Pharmaceuticals L.P., maker of gefitinib, which is indicated for advanced or metastatic NSCLC only in patients who respond to it.

Gefitinib and erlotinib are tyrosine kinase inhibitors that target EGF-R. Since somatic EGF-R mutations were discovered in 2004, retrospective studies cited by the two investigators have found that most lung cancer patients with these mutations respond to the two therapies.

The mutations are more common, Dr. Sequist noted, in women and in people with East Asian genetic heritage, with little or no history of smoking, and with adenocarcinoma histology (possibly with features of bronchioloalveolar carcinoma). About 10% of lung cancer patients in North America and Western Europe harbor the mutations; they are 2-3 times more prevalent in Asia.

Dr. Sequist and her colleagues screened tumor samples from 98 advanced NSCLC patients over 23 months. They found 34 patients with mutations, the most common of which were an exon 19 deletion and a change on exon 21 known as L858R. Three patients declined gefitinib therapy, leaving 31 who were treated.

The population had a median age of 63 years, with a range of 26-88 years. A majority (19 patients) was female, and the same proportion had never smoked.

Adenocarcinoma was the most common histology, diagnosed in 21 patients. Another four patients had adenocarcinoma with features of bronchioloalveolar carcinoma.

Dr. Sequist reported that one patient had a complete response, 16 had partial responses, and 12 had stable disease after starting gefitinib. As of the last data collection, the response rate was 55%, progression-free survival was 11.4 months, and overall survival was 20.8 months. Nearly half (46%) of the patients had not progressed at 1 year.

However, 11 patients had died, and 4 were found to have genetic mechanisms that made them resistant to a tyrosine kinase inhibitor targeting EGF-R. Fluorescence in situ hybridization (FISH) did not enhance the predictive value of the mutation analysis.

The Spanish study focused on an obstacle to screening NSCLC patients for genetic mutations: Many patients presenting with advanced disease do not have sufficient tumor tissue for genotyping. Dr. Morán and her colleagues found either exon 19 or exon 21 mutations in the tissue of 240 of 1,834 patients (13.1%) screened. The investigators then paired tissue and serum samples for 121 patients, of whom 84 also had mutations in their serum samples.

"The assessment of EGF-R mutations in serum is a valid method in the absence of available tumor tissue, with a sensitivity of 69.4%," said Dr. Morán.

At a median follow-up of 9 months, she reported that 54 patients with exon 19 deletions had slightly better responses to erlotinib than did 30 patients with L858R mutations (9 complete responses and 19 partial responses vs. 2 complete responses and 13 partial responses in the smaller cohort). The only significant difference, however, was that the exon 19 patients were younger, with a median age of 63 years vs. 71 years.

Discussant Dr. Vincent A. Miller of Memorial Sloan-Kettering Cancer Center in New York said the two trials presented promising survival results in a rapidly evolving field, and that the results of other ongoing phase III trials are eagerly anticipated. His own institution collects tissue samples routinely after surgery to screen for EGF-R and KRAS mutations. More sensitive tests will be developed, he predicted: "I don't think it's a question of 'if.' It's a question of 'when,' cost, and turnaround time." ■

Past Public Health Steps Offer Lessons for Future Pandemics

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

Cities that were able to implement and execute an early, sustained nonpharmaceutical response to the 1918-1919 influenza pandemic experienced lower mortality from the disease, investigators reported in the Aug. 8 issue of the Journal of the American Medical Association.

The three public health interventions that worked so well during the pandemic—quarantining ill, exposed, and possibly exposed persons; closing public schools; and banning public gatherings—would be just as important in any future pandemics, wrote Dr. Howard Markel of the University of Michigan, Ann Arbor, and his coauthors.

"Our study suggests that nonpharmaceutical interventions can play a critical role in mitigating the consequences of future severe influenza pandemics and should be considered for inclusion in contemporary planning efforts as companion measures to developing effective vaccines and medications for prophylaxis and treatment," they wrote (JAMA 2007;298:644-54).

The researchers examined the effect of public health interventions instituted in 43 of the nation's most highly populated cities during one 24-week period (Sept. 8, 1918, to Feb. 22, 1919). All data were extracted from historical records, including the U.S. Census Bureau's Weekly Health Index, public health documents, and state and federal reports.

Overall, there were 115,340 excess deaths from pneumonia or influenza during the time frame, or a rate of 500/100,000 population.

Every city enacted at least one of the three studied interventions, and 15 cities applied all three of them concurrently. The most common combination of interventions was school closure and a ban on public meetings, for a median duration of 4 weeks (34 cities; 79%). Most cities (40; 93%) implemented school closure in combination with another intervention, although three cities never closed schools at all. Overall, 25 cities closed schools just once, 14 closed them twice, and one city closed its schools three times. The median school closure time was 6 weeks.

Fifteen cities (35%) implemented all three interventions simultaneously.

The initial analysis showed that layered interventions were significantly associated with lower weekly death rates. The most effective combination was school closure and a public gathering ban.

Timing was also an important factor in reducing the death rate, the authors noted. Cities that implemented their interventions earlier in the disease cycle showed lower peak mortality, greater delays in reaching peak mortality, and lower total mortality.

They offered Pittsburgh as an example of a city that enacted interventions late and did not layer them. The Pennsylvania health department demanded a public gathering ban on Oct. 4, 1918, but city officials didn't close schools until Oct. 24. A week later, on Nov. 2, the state rescinded the public gathering ban. Pittsburgh's cumulative excess mortality of 807/100,000 population was the highest in the study, ranking the city 43rd of the 43 studied.

©USA Library of Congress/Photo Researchers

Nurses conduct a demonstration at the Red Cross Emergency Ambulance Station in Washington during the 1918 influenza pandemic.

Finally, they wrote, a sustained response was a crucial factor in keeping deaths down. The 21 cities that had the earliest implementation and most days of interventions had a significant reduction in influenza mortality, compared with the 21 cities that had later implementation and fewer days of interventions.

In fact, easing up on the interventions prematurely was associated with a double peak of disease. "We found no example of a city that had a second peak of influenza while the first set of nonpharmaceutical interventions was still in effect. …In dual-peaked cities, activation of interventions was followed by a diminution of deaths and, typically, when nonpharmaceutical interventions were deactivated, death rates increased," the authors wrote. "The 1918 experience suggests that sustained nonpharmaceutical interventions …need to be 'on' throughout the particular peak of a local experience," they concluded. ■

Radio Surgery Shows Promise For Inoperable Stage I NSCLC

BY MITCHEL L. ZOLER
Elsevier Global Medical News

WASHINGTON — Stereotactic radio surgery was a safe and reasonably effective alternative treatment for inoperable, stage I non–small cell lung cancer in a series of 21 patients at one center.

Based on these results and reports on the same treatment from other centers, it's reasonable to launch a study to compare stereotactic radio surgery with other treatments for inoperable patients with stage I NSCLC, Dr. Arjun Pennathur said at the annual meeting of the American Association for Thoracic Surgery.

Dr. Pennathur, a thoracic surgeon at the University of Pittsburgh, and his associates use a CyberKnife system, and they usually treat a patient with more than 100 individually delivered radiation beams; treatment takes 60-90 minutes. A dynamic tracking system monitors breathing motion and synchronizes the beam's location to the breathing. Treatment is guided by fiducial markers placed in and around the tumor with CT guidance.

The median dose was 20 Gy, which corresponds to an effective biologic dose of more than 70 Gy.

The series included 14 patients with stage IA disease and 7 with stage IB disease. The average tumor size was 2.2 cm, and the patients were about 70 years old.

The most common treatment complication was pneumothorax (10 patients). No treatment-related deaths occurred. Initial responses included complete response (seven cases), partial response (five), stable disease (five), and disease progression (three); one patient could not be evaluated. Local progression recurred in nine patients (43%) at a median of 12 months after treatment. Eleven patients were alive after a median follow-up of 21 months. The 1-year survival rate was 81%, and the 2-year rate was about 60%.

Although stereotactic radio surgery is still being refined, these results suggest it is superior to no treatment of stage I inoperable NSCLC, which has been documented to have a median survival of 14 months. ■

Dr. Robert Cerfolio, FCCP, comments: *Dr. Pennathur and associates have provided some early but important data from the United States that is similar to previous data reported recently from Japan. The authors' study suggests that stereotactic radio surgery, or what is most commonly delivered by the Cyberknife system in the United States, may provide improved results over external beam radiation for patients with stage I NSCL cancer who are not surgical candidates. The key is to ensure that patients are "really not surgical candidates," which means they have been denied surgery by at least two general thoracic surgeons who perform a large volume of lung surgery and that the patient's lymph nodes are pathologically negative. The issue of pneumothorax from fiducials may be resolved in the near future.*

Families Overriding Organ Donation Plans

ORLANDO — Patient wishes for organ donation were overridden by their families in about 20% of cases, according to research conducted at a level I trauma center in Charlotte, N.C.

Dr. A. Britton Christmas and colleagues at the F.H. Sammy Ross Jr. Center at the Carolinas Medical Center reviewed 3 months of organ donation referrals at their center. About 17 potential transplant recipients did not receive organs because a patient's previous donation intentions were overridden by family members, they wrote in a poster at the annual congress of the Society of Critical Care Medicine.

The researchers compared information from medical charts with data from the state department of motor vehicles (DMV) related to organ donation designations.

They analyzed information on 84 individuals who had DMV information on file and whose families had been approached by hospital staff for organ donation over the 3-month period. In the DMV records, 25 individuals were listed as organ donors, and 59 had not designated organ donation. For the 25 individuals designated as organ donors, 20 consents for donation were obtained from family members. Of the other 59 individuals, 22 consents were obtained.

The researchers estimated that the five individuals whose consent was withdrawn by the families resulted in 17 potential organ recipients who would not receive organs.

—Mary Ellen Schneider

For additional information on organ donation and the donor shortage, visit www.organdonor.gov.

Thomas L. Petty, MD, Master FCCP Endowment in Lung Research

A Legacy in Pulmonary Medicine

Considered a "Father of Pulmonary Medicine," Thomas L. Petty, MD, Master FCCP, is a recognized leader in chest medicine and outstanding contributor to the ACCP.

To honor Dr. Petty's accomplishments, The CHEST Foundation, in partnership with Boehringer Ingelheim, Inc., has established the Thomas L. Petty, MD, Master FCCP Endowment in Lung Research to support lung research and advances in patient care.

Donate to this important fund today by contacting The CHEST Foundation.
www.chestfoundation.org
(800) 343-2227 or (847) 498-1400

A Tribute to a Leader
Plan to attend The CHEST Foundation's Making a Difference Awards Dinner, where Dr. Petty will be honored.
Making a Difference Awards Dinner
Saturday, October 20, 2007
Chicago Cultural Center, Chicago, Illinois

Register online.
www.chestfoundation.org
Contact Teri Ruiz for more information.
truiz@chestnet.org or (847) 498-8308

THE CHEST FOUNDATION

The Science and Practice of Sleep Medicine

SLEEP Medicine

The Best Clinical Sleep Update of the Year **2008**

January 10-13
The Scottsdale Plaza Resort
Scottsdale, AZ

Plan to attend this 4-day review of the fundamentals of the science and clinical practice of sleep medicine. Designed for chest physicians, Sleep Medicine 2008 will offer relevant, practical instruction to help you improve your knowledge of sleep medicine and your patient care skills.

Study relevant topics, including sleep apnea, narcolepsy, restless legs *syndrome, insomia, para*somnias, and circadian rhythm disorders.

Review the latest technology and tools available as diagnostic resources.

Attend case management workshops led by leading experts.

Register Early and Save

Visit our Web site for details, or contact ACCP Customer Relations.

www.chestnet.org
(800) 343-2227 or (847) 498-1400

Sleep Institute
American College of Chest Physicians

AMERICAN COLLEGE OF CHEST PHYSICIANS

Pulmonary Perspectives

New IDSA/ATS Guidelines for Community-Acquired Pneumonia

The new Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) consensus guidelines for community-acquired pneumonia (CAP) have recently been published (Mandell et al. *Clin Infect Dis* 2007; 44 [suppl]:S27) and are available online at www.thoracic.org/sections/publications/statements/pages/mtpi/idsaats-cap.html. One of the major benefits of this set of guidelines is that it represents the consensus of both societies and avoids some of the real and perceived differences between the societies' earlier independent versions.

Several aspects of the new guidelines are unique or represent a significant change from earlier guidelines. One change is in the format of the recommendations. Now, there is not only a grading of the scientific evidence, but also an evaluation of the strength of each of the recommendations.

The new guidelines are organized around the critical admission decision(s). Both the Pneumonia Severity Index (PSI) and the British Thoracic Society's CURB-65 score (Confusion, Uremia, Respiratory rate, Blood pressure, and age > 65 years) have value in determining which patients may safely be treated as outpatients. However, both PSI and CURB-65 must be supplemented with additional clinical information, including oral intake ability, reliability of taking medications, returning for care if a condition worsens, and concomitant unstable medical conditions.

There is a major change in the guidelines for the criteria for severe CAP, which requires initial admission to the ICU. The guidelines committee felt that none of the previously available criteria for ICU admission was helpful in decision making, especially if the patient was not intubated or receiving vasopressors in the ED. Therefore, a new set of nine minor criteria was developed (see list of criteria). If a patient has three or more of the minor criteria, ICU admission should be considered, even if the patient is not intubated or receiving vasopressors—major criteria that would automatically deserve ICU admission. This new set of minor criteria needs prospective validation. The goal of the new criteria is to attempt to identify patients who are initially admitted to a general medical floor, but then require transfer to the ICU within 24 h of admission for hypotension or respiratory failure.

Recommendations for the extent of diagnostic testing to define the microbial etiology were determined predominantly by the site-of-care decision. Outpatients should be treated empirically in the majority of circumstances. In contrast, patients with severe CAP who require ICU admission should have an extensive diagnostic workup. Not only are diagnostic test results more likely to be positive in patients with severe CAP, there is an increased likelihood that the cause of CAP is a microorganism not covered by the usual empiric therapy. For patients admitted to non-ICU settings, diagnostic testing was not routinely recommended but should be done selectively for a variety of predisposing conditions (see list of indications). One example is the attempt to obtain a sputum specimen in a patient with severe COPD and a productive cough, because of the increased risk of infection with *Pseudomonas aeruginosa* as the etiology of CAP. The guidelines also encourage the use of rapid urinary antigen tests for *Legionella pneumophilia* and *Streptococcus pneumoniae* in patients with severe CAP. Cultures also are recommended for urinary antigen-positive cases because of the epidemiologic implications for infection with Legionella (to establish whether part of cluster requires positive cultures) and the antibiotic resistance pattern for pneumococcus.

Minor Criteria for Severe CAP

ICU admission should be considered if patients with CAP have three or more of these criteria:

- Respiratory rate ≥ 30 breaths/min
- Hypothermia (core temperature < 36°C)
- Hypotension requiring aggressive fluid resuscitation
- Confusion/disorientation
- Multilobar infiltrates
- $PaO_2/FIO_2 \leq 250$
- Uremia (BUN > 20 mg/dL)
- Leukopenia (WBC count < 4,000 cells/μL)
- Thrombocytopenia (platelet count < 100,000 cells/mm^3)

The recommended antibiotic regimens have not changed significantly. One of the controversial areas is the need for cephalosporin-based combination therapy for patients with severe CAP. To my knowledge, only one study has addressed this issue. The study excluded patients with shock but did include patients with respiratory failure. There was a trend toward worse outcomes when fluoroquinolone monotherapy was used for patients with respiratory failure. This suggested that previous recommendations by both societies, that combination therapy should be given to all patients with severe CAP, be maintained. Initial combination therapy was also recommended for patients with possible bacteremic *S pneumoniae* CAP, based on several prospective observational studies and retrospective analyses. Several options for treatment are offered within each group of patients with CAP, because one of the guidelines' main emphases is to avoid the use of an antibiotic that was previously prescribed for the patient.

An earlier decision to group health-care-associated pneumonia (HCAP), found particularly in nursing home patients, with hospital-acquired pneumonia in a different guideline from both societies made antibiotic recommendations slightly easier for the CAP statement. While *P aeruginosa* does cause regular CAP, the frequency is significantly less when patients with HCAP are excluded. The main risk factor is structural lung disease, including severe COPD. The new guidelines acknowledge that *P aeruginosa* CAP may be as common in patients admitted to non-ICU settings as it is in patients in the ICU.

Conversely, the role of methicillin-resistant *Staphylococcus aureus* (MRSA) did not diminish when HCAP patients were excluded. The main concern is the emergence of a community strain within many large cities. This community-acquired MRSA (CA-MRSA) strain is often associated with toxin production and a resultant necrotizing pneumonia. Vancomycin and linezolid were listed as recommended treatments, although little data exist on their efficacy for the CA-MRSA strain. All of the publications to date suggest that CA-MRSA CAP is a severe pneumonia, usually requiring ICU admission. Positive blood, pleural fluid, and/or respiratory tract cultures are the rule. Empiric MRSA coverage should, therefore, be limited to hospitals with known CA-MRSA in the community and stopped when cultures return negative for MRSA.

The new consensus guidelines also were the first to address nonantibiotic treatment of CAP. The strongest evidence was for the use of noninvasive ventilation in patients who were not severely hypoxemic and/or developing ARDS. A subgroup analysis of larger studies suggests that low tidal volume ventilation for patients with CAP-induced ARDS and the use of drotrecogin alfa activated for severe CAP be considered.

The new consensus guidelines built upon the earlier work done by members of the IDSA and the ATS. Not only has the science of guideline development evolved, but information regarding CAP management is constantly expanding. Severe acute respiratory syndrome (SARS) is not discussed in these guidelines; however, avian influenza and CA-MRSA are discussed. In recognition of a need for more prospective studies to address controversial areas and the always-changing bacterial resistance, both societies are committed to regular updates of these guidelines. ■

Dr. Richard G. Wunderink, FCCP
Feinberg School of Medicine,
Division of Pulmonary and Critical Care
Northwestern University
Chicago, IL

Clinical Indications for Extensive Diagnostic Testing

1. Severe CAP (BC, ETA, Sp, PUA, LUA, possibly BAL)
2. Failure of outpatient therapy (Sp, LUA, PUA)
3. Cavitary infiltrates (BC, Sp, fungal and tuberculosis cultures)
4. Leukopenia (BC, PUA)
5. Active alcohol abuse (BC, Sp, LUA, PUA)
6. Chronic liver disease (BC, PUA)
7. Severe COPD/structural lung disease (Sp)
8. Asplenia (BC, PUA)
9. Recent (within 2 weeks) travel (LUA)
10. Pleural effusion (BC, Sp, LUA, PUA, pleural fluid culture [PUA and LUA can be done on pleural fluid])
11. Positive Legionella urinary antigen (Sp)
12. Positive Pneumococcal urinary antigen (BC, Sp)

BAL = bronchoalveolar lavage, either bronchoscopic or nonbronchoscopic; BC = blood culture; ETA = endotracheal aspirate culture; LUA = Legionella urinary antigen; PUA= pneumococcal urinary antigen; Sp = sputum culture

Editor's Insight

Dr. Wunderink provides a wonderful insight into the unique aspects of the most recent version of the CAP guidelines.

In addition to presenting a unified document that represents both the IDSA and the ATS, the guidelines represent important steps forward in areas such as severity categorization (*ie*, Which patient has severe CAP?), recognizing atypical pathogens (*ie*, Is a patient infected with *P aeruginosa* or MRSA?), and nonantibiotic treatments (*ie*, Should a patient receive drotrecogin alfa activated or noninvasive intermittent positive pressure ventilation?). For clinicians, Dr. Wunderink's comments are a helpful navigational tool for the new guidelines.

—Editor

DR. GENE L. COLICE, FCCP
Editor,
Pulmonary Perspectives

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS®

PRESIDENT'S COMMENTARY

Dr. Friedrich Wegener, the ACCP, and History

On June 1, 2007, Stephen S. Lefrak, MD, FCCP, Professor of Medicine, Associate Dean and Director of the Humanities Program in Medicine at Washington University School of Medicine, wrote to Richard S. Irwin, MD, FCCP, *CHEST* Editor in Chief, about setting the record straight on the American College of Chest Physicians having given a "Master Clinician Award" to Friedrich Wegener, MD, at the ACCP Convocation in 1989.

BY DR. MARK J. ROSEN, FCCP

Dr. Wegener is renowned for his description and investigations of the necrotizing granulomatous vasculitis that we know as "Wegener's granulomatosis." What we did not know is that Wegener had ties with the Nazi party at its inception, and that he was an official in the army and a pathologist in Lodz, the site of a notorious Jewish ghetto from the time of the German invasion of Poland in 1939 until he fled with thousands of other Germans in 1945.

Dr. Lefrak asked that we set the record straight "for the historical record as well as the College's integrity." I will present the facts as we know them and what the ACCP leadership has done thus far regarding them.

Dr. Irwin forwarded that letter to me and to Alvin Lever, ACCP CEO and Executive Vice President.

First we checked the facts. There are a few articles on the subject, and this summary of the facts is abstracted from two articles in the peer-reviewed literature, both by Dr. Alexander Woywodt and colleagues. [1,2]

Their research revealed the following: Friedrich Wegener was born in 1907 in a small town in Germany, and his father was a surgeon. Dr. Wegener's career and the rise of the National Socialist party proceeded in parallel.

Wegener completed his medical studies in 1932, and in September 1932, he became a member of the Sturm Abteilung, or brownshirts. Hitler seized power on May 1, 1933, and Wegener joined the National Socialist party on the same day.

That year, he assumed his first academic position as "junior assistant" in the Department of Pathology at the University of Kiel. His chairman and mentor was Dr. Marin Staemmler, who had strong ties to the regime and published and lectured extensively on racial hygiene.

While the Nazis consolidated their power, started to implement their ideology, and brought on World War II, Wegener studied and published on necrotizing granulomatous inflammation.

Wegener served as an army pathologist in Lodz, arriving there on September 19, 1939, 18 days after the start of the German invasion of Poland. On December 10, a Jewish ghetto was established in Lodz, with the goal of deporting Jews and making the city *Judenrein* (free of Jews); in fact, most of the deportations were to the death camps, the remaining population becoming a source of slave labor.

There are apparently conflicting reports as to whether Wegener also served as a pathologist in the municipal health office (Gesumdheitsamt); that agency issued reports on 50 to 100 autopsies each month, the same time that ghetto residents suffered from the cold, disease, and famine, of which an estimated 43,000 people in the ghetto are believed to have died.

Wegener contracted diphtheria in 1944 and stopped work for a year, after which he assumed the role of field surgeon until he was captured by American forces.

While several of Wegener's contemporaries were implicated in selecting victims to be killed, or actually participating in atrocities, he was not. Wegener's name appeared on a Polish Ministry of the Interior registry of war criminals, but he never faced charges, and his files are no longer recoverable.

Our own inquiries to the National Archives and Records Administration (NARA), which include the records of the Berlin Document Center and the Simon Wiesenthal Center, yielded no evidence of Wegener's participation in war crimes.

Wegener spent a short time as a prisoner of war, followed by agricultural work, and later he resumed his career as a pathologist in Lübeck, Germany. An article on "Wegener's granulomatosis" was published in 1954, Wegener resumed an academic career in 1964, and he published his own review of "his" disease in 1967, before transitioning to private practice in 1970.

He went on to attend scientific meetings and found a patient support group. And the College gave him an award in 1989: the only record of this occurrence is in the Convocation Program printed that year. Wegener died in 1990.

How should we judge Friedrich Wegener today? I have no doubt that this issue will provoke intense controversy among all who care to consider it. It is indisputable that Friedrich Wegener was an early member of the brownshirts and Nazi party. As a pathologist in Lodz while thousands died in the ghetto, it defies reason that he did not know the consequences of Nazi ideology. To our knowledge, he never renounced or expressed regret for his official embrace of the Nazi party or involvement in its machinery.

Nevertheless, there is no evidence that he was involved directly in war crimes. By today's standards, any participation in the evil Nazi enterprise could be considered immoral and reprehensible. In that case, Wegener was either a "true believer" and evil himself or a shameless careerist worthy of our approbation.

However, there is no evidence of Wegener being an openly ardent ideologue, and no agency has found evidence of his committing a single "war crime," despite decades of intensive review.

I believe that Wegener probably did what millions of other Germans did: he went along with other Germans living through an economic disaster following the treaty of Versailles, eager to support new and strong leadership on behalf of their country. A recent medical school graduate, he was probably happy to overlook the dark side of the rise of Germany as his own career flourished.

Because Wegener the pathologist surely must have known the impact of Nazi policies on the people in the ghetto of Lodz, I believe that he is more culpable than others who looked the other way while the atrocities went on.

What should the ACCP do about the 1989 award to Dr. Wegener? This provoked difficult introspection and debate within the Executive Committee of the ACCP Board of Regents. Many of us spent hours considering this, and I have gone back and forth on the issue myself.

First, an investigation of the origin of the award showed that it was conferred only on this one occasion. It seems that a group of Wegener's friends and colleagues knew that he was approaching the end of his life and wanted to honor his contributions to medicine formally and publicly.

For the 1989 Convocation, the ACCP leadership, unaware of his connections with the Nazi party and activities during the war, "made up" a "Master Clinician" award, which was never bestowed before or since. We asked some ACCP members involved in that decision for their perspective, and they insist that they did not know of Wegener's past, and agree that if they had known, there would have been no such award.

We discussed whether the award should be taken away posthumously.

Continued on following page

This Month in *CHEST*: Editor's Picks

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

▶ **Transition From Intravenous Epoprostenol to Subcutaneous Treprostinil in Pulmonary Arterial Hypertension: A Controlled Trial.** *By Dr. M. Rubenfire, et al*

▶ **Apical and Midventricular Transient Left Ventricular Dysfunction Syndrome (Tako-Tsubo Cardiomyopathy): Frequency, Mechanisms, and Prognosis.** *By Dr. K. Volkhard, et al*

▶ **ACCP Evidence-Based Guideline Development: A Successful and Transparent Approach Addressing Conflict of Interest, Funding, and Patient-Centered Recommendations.** *By Dr. M. H. Baumann, FCCP, et al*

▶ **Diagnosis and Management of Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd edition)** – *CHEST Supplement*

▶ **Venous Thromboembolism Prophylaxis in Acutely Ill Hospitalized Medical Patients: Findings From the International Medical Prevention Registry on Venous Thromboembolism.** *By Dr. V. F. Tapson, FCCP, et al*

▶ **Point/Counterpoint POINT: The Ethics of Unilateral DNR Orders: The Role of "Informed Assent."** *By Dr. J. R. Curtis, FCCP, and R. A. Burt, JD*

COUNTERPOINT: Is It Ethical To Order "DNR" Without Patients' Consent? *By Dr. C. A. Manthous, FCCP*

REBUTTALS: *By Dr. J. R. Curtis, FCCP, and R. A. Burt, JD; and Dr. C. A. Manthous, FCCP.*

www.chestjournal.org

AMERICAN COLLEGE OF CHEST PHYSICIANS®

NEWS FROM THE COLLEGE

Continued from previous page

There were passionate and persuasive arguments that Wegener should have not taken a commission in the army, and should have declined or resigned from his appointment in Lodz.

Others reflected the Committee's consensus that revoking an award that reflects Wegener's indisputable scientific achievements absent evidence of direct involvement in war crimes would not be appropriate.

The young and no doubt ambitious Wegener made very poor choices in embracing a heinous movement and serving the German war effort for which his mentor and chairman was an enthusiastic participant. On the other hand, half of German doctors were members of the Nazi party during the war.

By analogy, George Washington and Thomas Jefferson were slave owners, but their images are still on Mount Rushmore and our currency.

In the end, the Executive Committee elected to inform the membership about the facts of Wegener's past, about the facts of the award the College gave him, and about what we will do to prevent a similar episode.

My opinion. Speaking for myself, I can only conclude that Wegener was, at best, deeply flawed and collaborated with very bad people in a bad cause to maintain and advance his career.

How can any of us be sure we would not have done the same thing in that situation? I hope I would have had the courage and conscience to resign and end such a career, but how could I know? That Wegener did autopsies and saw the consequences of Nazi philosophy makes him especially culpable.

Judging with 21st century sensibilities and perfect hindsight, I am reconciled to the decision that withdrawing an improvised award 17 years after the fact for a person's actions 45 or 50 years before dignifies the award more than it deserves. It accomplishes little other than to affirm that the ACCP condemns the actions of Nazis and those who supported them, and that should be obvious enough and not need a symbolic action.

I personally regret deeply that the College unknowingly bestowed an award to a former Nazi who surely took part in some way in support of the Holocaust and apologize to the families and memories of its victims.

How would current ACCP policies prevent another situation like this? First, I am certain that no ACCP awards committee would ever consider a candidate with ties to the Nazi party or any other hate group. The College also precludes granting awards to scientists who serve the tobacco industry and to any other enterprises that conflict with the College's core values.

In addition, I believe we have learned not to devalue formal ACCP recognition by inventing an award for single use, especially when it is a "gold watch" in anticipation a colleague's retirement or imminent death.

These have been difficult issues for us to consider. They will probably provoke considerable controversy, and they should.

As this will be discussed by the ACCP Board of Regents in October, I invite you to submit comments to me directly at mrosen@chestnet.org. We will publish some of these comments in future issues as best as we can. ■

1. Woywodt A, Haubitz M, Haller H, et al. Wegener's granulomatosis. Lancet 2006; 367:1362-1366
2. Woywodt A, Matteson EL. Wegener's granulomatosis: probing the untold past of the man behind the eponym. Rheumatology 2006; 45: 1303-1306

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Medical Information Section at Exhibit Booths

BY KATHRYN B. LUCAS

Director, Professional Relations and Education, Boehringer Ingelheim Pharmaceuticals, Inc.

It was recently brought to the attention of the ACCP Industry Advisory Council that not all convention attendees understand the purpose of the medical information section of a promotional exhibit. In their commitment to the free exchange of scientific information between health-care professionals, pharmaceutical companies deploy medical information teams to leading medical conferences in order to respond to unsolicited inquiries from health-care professionals.

The medical information staff consists of trained health-care professionals who uphold the highest professional standards of rigor and integrity in addressing the health-care community and in disseminating nonpromotional medical information upon request.

Through the medical information booths at conferences, the pharmaceutical companies invite, encourage, and sustain the free exchange of scientific information between health-care professionals—a cornerstone of medical research, innovation, and progress. ■

AMERICAN COLLEGE OF CHEST PHYSICIANS®

NEWS FROM THE COLLEGE

The Ambassadors Group—CHEST 2007 Events

▶ **Sunday, October 21—"Train the Trainer" Session,** *2:30 PM – 4:00 PM*
The CHEST Foundation provides tobacco prevention health education and encourages lung health among youth. In this interactive session, Susan Kvale, with the help of Monir Almassi and Kathy Wilder, will demonstrate antismoking teaching methods for children in fifth grade, as part of the Lung Lessons℠ curriculum. Monir also will distribute a flyer to attendees about how to organize a 5K run for teenagers.

THE CHEST FOUNDATION℠
AMBASSADORS GROUP

▶ **Monday, October 22—Global Outreach Tea,** *3:30 PM – 5:00 PM*
The Ambassadors Group fourth annual Global Outreach Tea is a great opportunity to socialize and learn more about the Ambassabors Group.

▶ **Tuesday, October 23—Annual Open Meeting,** *9:30 AM – 11:30 AM*
Everyone is invited to the Ambassadors Group Annual Open Meeting to learn more about our programs and help us brainstorm plans for future activities. Come, and bring a friend! Meet the 2007 Ambassadors Group Humanitarian Recognition Award recipient, Mr. Al Keith, CEO and Founder of CTK Clinical Consultants, LLC.

▶ **Tuesday, October 23—Designology (Hospitality and Information Room),** *4:00 PM – 5:00 PM*
Meet the designers from Susan Fredman & Associates, one of Chicago's leading interior design firms, and discover how the experts reveal *your* design aesthetic. Learn how to make the best choices for your home and lifestyle by understanding how you live, more than knowing simply what you like.

▶ **Wednesday, October 24—Resculpt Your Lifestyle (Hospitality and Information Room),** *2:30 PM – 4:00 PM*
Perhaps, it is time to resculpt your lifestyle before your health and body take on the shape of that comfy old couch! Discover the secrets to staying in shape at any age at this exciting, innovative, and interactive program by Marla Richmond, MS, exercise physiologist and author.

▶ **Membership:** Join the Ambassabors Group or renew your membership now, and you'll be a member through CHEST 2008. Sign up and pay online at www.chestfoundation.org.

▶ **Ambassadors Group Membership Directory:** A membership directory will be distributed to Ambassadors Group members by mid-November, as an e-mail attachment. You are encouraged to respond with your edited contact information to Kathy Wilder at wilderkw@ak.net, *even if all information is correct*. If you are a new or current member, and have not received your directory from Kathy through e-mail, contact her directly. ■

Ambassadors Group Hospitality and Information Room
(Open Hours)
Chicago Marriott Downtown – Lincolnshire Room
Saturday, October 20
1:00 PM – 5:00 PM
Sunday, October 21
2:00 PM – 5:00 PM
Monday, October 22
1:00 PM – 3:00 PM
Tuesday, October 23
1:00 PM – 5:00 PM
Wednesday, October 24
1:00 PM – 5:00 PM

Xolair® Omalizumab FOR SUBCUTANEOUS USE

BRIEF SUMMARY
Please see package insert for Full Prescribing Information.

WARNING
Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair administration, and health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur *(see WARNINGS, and PRECAUTIONS, Information for Patients).*

INDICATIONS AND USAGE
Xolair (Omalizumab) is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

CONTRAINDICATIONS
Xolair should not be administered to patients who have experienced a severe hypersensitivity reaction to Xolair (*see WARNINGS: Anaphylaxis*).

WARNINGS
Anaphylaxis
Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Xolair should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports *(see ADVERSE REACTIONS)*. Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur *(See PRECAUTIONS, Information for Patients)*.

Xolair should be discontinued in patients who experience a severe hypersensitivity reaction *(see CONTRAINDICATIONS)*.

Malignancy
Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

PRECAUTIONS
General
Xolair has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

Corticosteroid Reduction
Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

Information for Patients
Patients receiving Xolair should be told not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Patients should be told that they may not see immediate improvement in their asthma after beginning Xolair therapy.

Parasitic (Helminth) Infection
In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Omalizumab-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Omalizumab than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups. Patients at high risk of geohelminth infection should be monitored for such infections while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

Laboratory Tests
Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Serum total IgE levels obtained less than 1 year following discontinuation may not reflect steady state free IgE levels and should not be used to reassess the dosing regimen.

Drug Interactions
No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at Omalizumab concentrations up to 5000 µg/mL.

The effects of Omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of Omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

Pregnancy (Category B)
Reproduction studies in cynomolgus monkeys have been conducted with Omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of Omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

IgG molecules are known to cross the placental barrier. There are no adequate and well-controlled studies of Xolair in pregnant women. Because animal reproduction studies are not always predictive of human response, Xolair should be used during pregnancy only if clearly needed.

Pregnancy Exposure Registry
To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established. Healthcare providers should encourage their patients to call 1-866-4XOLAIR (1-866-496-5247) to enroll in the Xolair Pregnancy Exposure Registry. Healthcare providers can call this number to obtain further information about this registry.

Nursing Mothers
The excretion of Omalizumab in milk was evaluated in female cynomolgus monkeys receiving SC doses of 75 mg/kg/week. Neonatal plasma levels of Omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of Omalizumab were 1.5% of maternal blood concentration. While Xolair presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that Xolair will be present in human milk. The potential for Xolair absorption or harm to the infant are unknown; caution should be exercised when administering Xolair to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use
In clinical trials 134 patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

ADVERSE REACTIONS
Clinical Trials Experience
The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies *(see WARNINGS)*. Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

In clinical trials the observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%).

The adverse reactions most commonly observed among patients treated with Xolair in clinical studies included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients. These were also the most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse reaction).

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

The data described above reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

Table 1 shows adverse events that occurred ≥1% more frequently in patients receiving Xolair than in those receiving placebo in the placebo-controlled asthma studies. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 1.

Table 1
Adverse Events ≥1% More Frequent in Xolair-Treated Patients

Adverse event	Xolair n=738 (%)	Placebo n=717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

Age (among patients under age 65), race, and gender did not appear to affect the between group differences in the rates of adverse events.

Injection Site Reactions
Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection-site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%). The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity
Low titers of antibodies to Xolair were detected in approximately 1/1723 (<0.1%) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

Postmarketing Spontaneous Reports
Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose,19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown. Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

Hematologic: Severe thrombocytopenia has been reported in postapproval use of Xolair.

Skin: Hair loss has been reported in postapproval use of Xolair.

OVERDOSAGE
The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period, which was not associated with toxicities.

MEDICATION GUIDE
XOLAIR®
(OMALIZUMAB)

IMPORTANT: XOLAIR SHOULD ALWAYS BE INJECTED IN YOUR DOCTOR'S OFFICE.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XOLAIR?
A severe allergic reaction called anaphylaxis has happened in some patients after they received Xolair. Anaphylaxis is a life-threatening condition and can lead to death so get emergency medical treatment right away if symptoms occur.

Signs and Symptoms of anaphylaxis include:
- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of "impending doom"
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Get emergency medical treatment right away if you have signs or symptoms of anaphylaxis after receiving Xolair.

Anaphylaxis from Xolair can happen:
- right after receiving a Xolair injection or hours later
- after any Xolair injection. Anaphylaxis has occurred after the first Xolair injection or after many Xolair injections.

Your healthcare provider should watch you for some time in the office for signs or symptoms of anaphylaxis after injecting Xolair. If you have signs or symptoms of anaphylaxis, tell your healthcare provider right away.

Your healthcare provider should instruct you about getting emergency medical treatment and further medical care if you have signs or symptoms of anaphylaxis after leaving the doctor's office.

WHAT IS XOLAIR?
Xolair is an injectable medicine for patients ages 12 and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is done to see if you have allergic asthma.

WHAT ELSE SHOULD I KNOW ABOUT XOLAIR?
- You should not receive Xolair if you have ever had an allergic reaction to a Xolair injection.
- Do not change or stop taking any of your other asthma medicines unless your healthcare provider tells you to do so.
- There are other possible side effects with Xolair. Talk to your doctor for more information. You can also go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Jointly marketed by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

(4840201)
Revision Date: July 2007

Reference: 1. XOLAIR [prescribing information]. South San Francisco, Calif: Genentech Inc; 2007.

Genentech | NOVARTIS

©2007 Genentech, Inc. and Novartis Pharmaceuticals Corporation

8121302 C-XOL-100027

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EDUCATION INSIGHTS

What's Happening at CHEST 2007?

BY ED DELLERT, RN, MBA
Vice President, Educational Resources
JENNIFER STAWARZ
Manager, Public Relations

If you have attended CHEST annual meetings in the past and have CHEST 2007 on your fall schedule this year (and we hope you do), you are likely to notice some changes.

The majority of these changes are related to the education curriculum, but more specifically, how we deliver and track continuing medical education (CME).

Learning Categories

We will be introducing the new **ACCP Learning Categories**, labels that will help you identify the types of educational opportunities being offered at CHEST 2007.

These new Learning Categories clearly specify the type of instruction and methodology used for each session, which will allow you to choose sessions related to your clinical interests, education goals, and learning style.

There are many theories and evidence in general higher educational literature that has led to the development of this ACCP learning taxonomy. The key to the **ACCP Learning Categories** is to provide a variety of educational opportunities.

The six learning categories are as follows:

- Learning Category I: Lecture-Based
- Learning Category II: Self-Directed
- Learning Category III: Evidence-Based
- Learning Category IV: Case- and Problem-Based
- Learning Category V: Simulation
- Learning Category VI: Quality Improvement

You will see these learning labels on the sessions you are attending at CHEST, and you will find them being identified in the Final Program (see the illustration above for an example).

5:00 AM - 8:00 AM
Session ID 541
Chicago Marriott Downtown, Grand Ballroom, Salon I
Satellite Symposium
Common Pulmonary Dilemmas in Clinical Updates
Registration and Breakfast 5:00 AM – 6:00 AM
Program 6:00 AM – 8:00 AM
Chair Victor F. Tapson, MD, FCCP, Durham, NC
Topics & Faculty
- The Evolution of Management of VTE and Its Sequelae
  Victor F. Tapson, MD, FCCP, Durham, NC
- Challenges in the Diagnosis and Treatment of COPD
  Bartolome R. Celli, MD, FCCP, Boston, MA
- Benefits of Early Diagnosis and Treatment of PAH: Data From the PAH Quality Enhancement Research Initiative (QUERI)
  Ronald J. Oudiz, MD, Torrance, CA

Summary Management of complex patients, such as those with venous thromboembolism (VTE), COPD, and pulmonary arterial hypertension (PAH), requires understanding of new and sometimes controversial results of clinical trials, with a background of existing guidelines. This educational gap will be addressed by this program. The symposium will explore therapeutic choices and appropriate selection of interventions to improve the diagnosis and management of VTE, COPD, and PAH in order to improve outcomes.

Objectives
During this activity, you will:
- Discuss the best therapeutic strategies for the management of patients with VTE, COPD, or PAH.
- Describe the diagnosis and treatment of VTE, COPD, and PAH.

ACCP Curricula *Pulmonary Manifestations of Systemic Disease, Pulmonary Vascular Disease*
ACCP Learning Category I *Lecture-Based*
MOL *Scope of Practice-Pulmonary Education*
Supported by an unrestricted educational grant from Actelion Pharmaceuticals.

The **ACCP Learning Categories** are being formally introduced at CHEST 2007, and they will be used to categorize all subsequent educational activities that the ACCP offers.

Maintenance of Licensure

You will also find that sessions have another category label, Maintenance of Licensure (**MOL**), identified by each session with areas related to state medical licensure, specifically relevant to the chest physician (see sample above).

Depending upon the state in which you practice, your requirements could include a set number of CME hours in general scopes of practice, but there is a growing trend to denote those CME hours into specific areas, such as ethics, end-of-life care, geriatrics, patient safety, and others.

When you obtain your CME certificate at CHEST 2007, you will notice that your total for CME hours is still listed, but the credit hours will be divided into the **ACCP Learning Categories** and the **MOL** hours from the sessions you attended.

Our hope is that this CME certificate will provide education documentation for your records or assist you in meeting institution requirements where you have privileges, state licensing documentation, certification requirements, or a combination of all of these areas.

Your CME certificate will resemble the sample to the right.

CME Evaluation and Certification—No More Paper

Another noticeable change at CHEST 2007 will be the process of how to evaluate sessions and, ultimately, obtain your CME certificate.

There will be no paper version of the evaluation form in your registration packets. There will be no paper form of a CME certificate to exchange at the registration desk.

What you will find, however, is that the evaluations document and the subsequent CME certificate will be available online through the ACCP Web site. Letters of attendance for our international attendees will also be available only on the Web site.

You can complete the online evaluation in several ways: special computers will be set up in the convention center for this use; you can use your own computer in any location you wish; or complete the task when you arrive home, at your convenience (just note that you will only have about 1.5 months following CHEST to complete this).

As you complete the form online, your CME certificate will be generated automatically. Just evaluate the sessions you attended, and we will automatically take care of the rest.

Once completed, the CME certificate is available for you to save electronically or print for your records. (Printers will not be available at CHEST.) Log back into our system anytime, and all of your CME activities and certificates will be archived for you to print off again.

There will be other noticeable changes at CHEST 2007, but we don't want to spoil the whole surprise for you. As the learning categories and MOL, evaluation, and CME certificate are different than what you might ex-perience in other educational venues outside of ACCP, we wanted you to have a chance to understand these new additions.

So when you leave CHEST 2007, you will have hopefully acquired new skills, knowledge, and/or attitudes that affect your clinical practice and help you meet your goals of lifelong learning. I look forward to hearing from you. Let us know what you think. See you Chicago!

For more information, contact Ed Dellert at edellert@chestnet.org.

AMERICAN COLLEGE OF CHEST PHYSICIANS
3300 Dundee Road • Northbrook, Illinois 60062-2348 USA
CME@chestnet.org • www.chestnet.org
Voice: (847) 498-8376 • Fax: (847) 498-5460

Continuing Medical Education Credit Certificate

John Stangel
9876 Oak Street
Suite 232
Arlington Heights, IL 69999
USA

CHEST 2007 October 20-25 2007 Chicago IL

Accreditation Statement
The American College of Chest Physicians is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation Statement
The American College of Chest Physicians designates this educational activity for a maximum of 38.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

ACCP's Learning Category:
The American College of Chest Physicians utilizes a six category learning system to encourage participants to reflect and document how their CME Credit Hours were obtained. ACCP Learning Categories specify the type of instruction and methodology used to deliver clinical information. Within each learning category, educational credit hours are identified as a mechanism to be used toward state licensing requirements, where applicable. This format reflects the types of education encountered during ACCP activities. Completion of any ACCP learning category does not constitute verification of an individual clinical competency.

Faculty CME Credit:
The American College of Chest Physicians may award *AMA PRA Category 1 Credit(s)™* to their faculty for teaching at designated live activities. This credit acknowledges the learning associated with the preparation for an original presentation. Faculty may be awarded two (2) *AMA PRA Category 1 Credit(s)™* for each hour they present at a live activity designated for such credit. Faculty may not claim simultaneous credit as physician learners for sessions at which they present; however, they may claim participant credit for other sessions they attend as learners at a designated live activity. Credit may only be claimed once for repeated presentations.

John Stangel, Designated as Physician, CHEST 2007	ACCP Learning Hours
ACCP Learning Category I Credits – Traditional Education and Learning	
a. Scope of Practice-Pulmonary Education	0.0
b. Scope of Practice-Critical Care Education	9.0
c. Scope of Practice-Sleep Medicine Education	0.0
d. Pain management and End-of-Life Care	0.0
e. Risk Management	0.0
f. Medical Errors and Patient Safety	0.0
g. Medical Ethics	0.0
h. Geriatrics	9.0
SUB-TOTAL	18.0
ACCP Learning Category II Credits – Self-Directed Learning	
a. Scope of Practice-Pulmonary Education	0.0
b. Scope of Practice-Critical Care Education	0.0
c. Scope of Practice-Sleep Medicine Education	4.5
d. Pain management and End-of-Life Care	0.0
e. Risk Management	0.0
f. Medical Errors and Patient Safety	0.0
g. Medical Ethics	0.0
h. Geriatrics	0.0
SUB-TOTAL	4.5
ACCP Learning Category III Credits – Evidence-Based Learning	
a. Scope of Practice-Pulmonary Education	0.0
b. Scope of Practice-Critical Care Education	2.0
c. Scope of Practice-Sleep Medicine Education	0.0
d. Pain management and End-of-Life Care	0.0
e. Risk Management	0.0
f. Medical Errors and Patient Safety	2.5
g. Medical Ethics	0.0
h. Geriatrics	0.0
SUB-TOTAL	4.5
ACCP Learning Category IV Credits – Case and Problem-Based Learning	
a. Scope of Practice-Pulmonary Education	3.0
b. Scope of Practice-Critical Care Education	0.0
c. Scope of Practice-Sleep Medicine Education	0.0
d. Pain management and End-of-Life Care	0.0
e. Risk Management	0.0
f. Medical Errors and Patient Safety	0.0
g. Medical Ethics	2.0
h. Geriatrics	0.0
SUB-TOTAL	5.0
ACCP Learning Category V Credits – Experimental Simulated Learning	
a. Scope of Practice-Pulmonary Education	0.0
b. Scope of Practice-Critical Care Education	0.0
c. Scope of Practice-Sleep Medicine Education	2.5
d. Pain management and End-of-Life Care	0.0
e. Risk Management	0.0
f. Medical Errors and Patient Safety	3.0
g. Medical Ethics	0.0
h. Geriatrics	0.0
SUB-TOTAL	5.5
ACCP Learning Category VI Credits – Quality Improvement Evaluation and Learning	
a. Scope of Practice-Pulmonary Education	0.0
b. Scope of Practice-Critical Care Education	0.0
c. Scope of Practice-Sleep Medicine Education	0.0
d. Pain management and End-of-Life Care	1.0
e. Risk Management	0.0
f. Medical Errors and Patient Safety	0.0
g. Medical Ethics	0.0
h. Geriatrics	0.0
SUB-TOTAL	1.0

CME Course credits: 38.5

Faculty CME credits: 11.5

Total *AMA PRA Category I Credit(s)™* (Issued on 11.20.2007): **50.0**

The American College of Chest Physicians certifies that _____has participated in the educational activity titled CHEST 2007 at McCormick Place, Lake Side Center, Chicago, Il and is awarded FILL IN NUMBER OF CREDITS *AMA PRA Category 1 Credit(s) TM*

Edwin L. Dellert, RN, MBA
Vice President, Educational Resources

AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

The Acute Kidney Injury Network: An Interdisciplinary Initiative

BY DR. JOHN A. KELLUM, FCCP
On Behalf of the AKIN Working Group

Acute kidney injury (AKI) is a common clinical problem defined as an injury or insult that causes an abrupt functional or structural change in the kidney. Recent studies have shown increased hospital mortality following AKI, and even minor short-term changes in serum creatinine (sCreat) are associated with increased mortality and/or accelerated progression of preexisting chronic kidney disease.

In order to foster the development of clinical practice recommendations, and to facilitate clinical and translational research in AKI, a group representing members from the Acute Dialysis Quality Initiative (ADQI), critical care, and nephrology societies recently established the Acute Kidney Injury Network (AKIN). The fundamental goal of this group is to ensure the best outcomes for patients with, or at risk for, AKI. The first AKIN conference, held in Amsterdam in September 2005, focused on the development of uniform standards for definition and classification of AKI.

Wide variation in definitions of acute renal failure has made it difficult to compare information across studies and populations. ADQI proposed the RIFLE criteria (risk [R], with injury [I], with failure [F], with sustained loss [L] and with end-stage [E] status) for classification of AKI, and these criteria have been validated in several studies.

However, recent evidence suggests that even small changes in sCreat values are associated with adverse outcomes in a variety of settings.

The proposed new criteria and staging are shown in the accompanying table and callout. The proposed staging system retains the emphasis on changes in sCreat values and urine output and corresponds to the risk, injury, and failure categories of the RIFLE classification, with the stage 1 criteria representing the new diagnostic criteria for AKI. These proposed standards will need to be validated in future studies.

AKIN described the five key elements that should be addressed by the professional communities involved in the care of patients with AKI: evaluation of the global epidemiology of AKI, delineation of clinically meaningful outcomes, development and implementation of strategies to improve outcomes, promotion of research studies, and assessment of the effectiveness of these collaborative approaches.

Watch for future updates on AKIN. A list of AKIN members can be found in *Crit Care* 2007;11:R31. ■

Classification/Staging System for AKI

Stage	Creatinine Criteria	Urine Output Criteria
1	Increase sCreat value = 0.3 mg/dL or increase 1.5 to 2 times baseline	< 0.5 mL/kg/h for > 6 h
2	Increase sCreat value > 2 but < 3 times baseline	< 0.5 mL/kg/h for >12 h
3	Increase sCreat value ≥ 3 times baseline (or sCreat ≥ 4.0 mg/dL with an acute rise of at least 0.5 mg/dL)	< 0.3 mL/kg/h x 24 h or anuria x 12 h

Modified from RIFLE criteria. From Mehta et al. Crit Care 2007;11:R31. Used with permission.

Elsevier Global Medical News

AKI Diagnostic Criteria

An abrupt (within 48 h) reduction in kidney function: absolute increase in sCreat value of either = 0.3 mg/dL, or a percentage increase of = 50% (1.5 times baseline), or a reduction in urine output (< 0.5 mL/kg/h for > 6 h).

PRODUCT OF THE MONTH

MOC Modules for Pulmonary and Critical Care Medicine

All American Board of Internal Medicine (ABIM) diplomats maintaining certification are expected to complete 20 points in self-evaluation of medical knowledge. To facilitate the completion of MOC by general internists and subspecialists, the ABIM provides multiple options: (1) ABIM Medical Knowledge Modules; and (2) self-assessment products developed by other organizations.

This ACCP product was developed as a derivative of the ACCP-SEEK program. Each module is a set of self-assessment questions to assist individuals in identifying strengths and weaknesses in their clinical knowledge. Each set of questions has been reviewed and approved by the ABIM for use in its MOC program.

To learn more, and to purchase each module, visit the ACCP online store at accp.chestnet.org/storeWA/StoreAction.do?method=view&pcrNum=9. ■

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

SLEEP STRATEGIES

Identifying, Preventing, and Reporting Drowsy Driving

According to the National Highway Traffic Safety Administration, at least 100,000 police-reported motor vehicle accidents annually are the direct result of driver fatigue, resulting in more than 1,550 deaths, 71,000 injuries, and $12.5 billion in diminished productivity and property loss.

Many crashes resulting from drowsy driving are underreported due to limited police training in detecting sleep-related accidents and the absence of mechanisms to report drowsiness on accident report forms.

According to the National Sleep Foundation's (NSF) 2005 "Sleep in America" survey, 60% of adult drivers reported driving while feeling sleepy within the past 12 months.

In the 2007 NSF survey, which focused on women and sleep, 37% of women between the ages of 18 and 24 reported driving drowsy at least once a month, while 31% reported driving drowsy during pregnancy. Thirty-eight percent of new mothers reported being fatigued, while behind the wheel, on a monthly basis.

In 2004, the AAA Foundation for Traffic Safety Internet survey reported that 90% of police officers in the United States and Canada pulled over drivers they suspected were drunk, but were, in fact, drowsy.

Sleep disorders that lead to driver fatigue include primary and comorbid insomnias, obstructive sleep apnea, and restless legs syndrome. Those at a particularly high risk include men aged 16 to 29; people who drive at night or alone; people with poor sleep hygiene; frequent travelers; shift workers; people who drive long, rural, dark, or "boring" roads; and individuals taking sedative medications.

The effects of driver fatigue include impaired vigilance, attention, and reaction time. Fatigued drivers are more likely to succumb to "road rage." Fatalities to the driver, passengers, and people in other vehicles may occur when sleep onset results in a complete loss of control of the motor vehicle.

Unlike the driver who is pulled over for driving while intoxicated, there is no "breathalyzer," blood test, or any other easy way to identify a person who is driving when drowsy. Physicians must depend upon patient reports of drowsiness by obtaining a history or by using diagnostic surveys, such as the Epworth Sleepiness Scale. Patients at high risk for drowsy driving should be questioned, and physicians should also determine if they have any recent history of motor vehicle accidents. Unfortunately, because the problem of drowsy driving is widespread and so many people "get away with it," as well as because many physicians also have poor sleep hygiene, there is an unfortunate tendency to minimize the problem.

Sleep Institute
American College of Chest Physicians

> Being awake for 18 hours is the same as having a blood alcohol concentration of 0.08%, which is legally drunk, leaving you at equal risk for a crash.
>
> —*From www.drowsydriving.org*

Prevention and Reporting

Regrettably, a patient's problem of drowsy driving may not come to a physician's attention until after a serious accident has occurred. Therefore, a proactive approach is required. Some of the best approaches include the identification of people at risk, followed by careful questioning and patient education. Public awareness campaigns, such as those sponsored by the NSF and the National Highway Safety Traffic Administration, have also been effective. The NSF is declaring November 5–11, 2007, Drowsy Driving Prevention Week™, a national public awareness campaign about the tragic consequences of driving while drowsy.

A number of state and federal legislative initiatives have focused on the physician's role in reporting impaired drivers. In 1999, the challenges of such reporting were noted by the American Medical Association's Council on Ethical and Judicial Affairs:

Physicians are in a unique position to anticipate the impact of physical and mental conditions on driving impairment . . . Motivated by a respect for the individual and a desire to promote patient autonomy, physicians traditionally have allowed the patient to make the ultimate decision whether to continue driving. The decision not to interfere with the patient's decision to drive also may derive from a physician's commitment to a patient's well-being. The privilege of driving is a source of freedom and empowerment for many individuals. Removing this privilege has its risks. The loss of the ability to be independently mobile can be a devastating psychological blow . . .

All states provide opportunities for physicians to report drowsy drivers. In 2007, reporting of drowsy drivers by physicians is generally voluntary. Proponents of mandatory reporting cite the physician's role in preventing injury and death in patients, as well as the traditional role of the physician in assisting with the promotion of public safety. Those who oppose mandatory reporting cite the difficulty in assessing drowsy driving.

The ethical responsibility of the physician to maintain patient confidentiality is another obstacle. The Health Insurance Portability and Accountability Act (HIPAA) privacy rule permits physicians to disclose protected health information, without individual authorization as "required by law" or to avert a serious threat to health or safety. Other state patient confidentiality statutes may supersede HIPAA's provisions.

The wide variety of people who drive while impaired makes mandatory reporting impractical. These drivers include the 60% of NSF survey respondents who report occasional drowsy driving; and the 25 million Americans who work rotating shifts; as well as people who are impaired based on other disorders, such as dementia, chronic alcohol or drug abuse, seizure disorders, visual disturbances, and advanced age. Mandatory reporting also may be a deterrent to candid patient-physician communication.

Alternatives to reporting a "drowsy driver" include having sincere discussions with patients and families regarding the risks of drowsy driving, as well as providing strategies to reduce those risks. Patients should be made aware that the issue is being documented as a permanent part of the medical record. The potential financial consequences of driving while impaired, "against medical advice," also can be emphasized.

Maggie's Law and Oregon Law

In 1997, Maggie McDonnell, a 20-year-old college student, was killed by a driver who crossed three lanes of traffic and crashed into her car directly from the front. The driver had not slept in 30 hours and had been using drugs. In the absence of any laws pertaining to drowsy driving, the driver received a suspended jail sentence and a $200 fine. Maggie's mother, Carole McDonnell, lobbied vigorously to make drowsy driving a criminal offense. In August 2003, New Jersey became the first state to consider a fatal accident by a drowsy driver as vehicular homicide: "For the purposes of this section, driving a vehicle or vessel while knowingly fatigued shall constitute recklessness. 'Fatigued,' as used in this section, means having been without sleep for a period in excess of 24 consecutive hours" (excerpt from 210th Legislature, State of New Jersey).

Current Oregon regulations make it mandatory for physicians to report impaired driving to the Oregon Department of Motor Vehicles (Oregon Administrative Rules, Division 74). Types of impairments that require physician reporting and may be experienced by drowsy drivers, include the following: decreased awareness, reduction in the ability to efficiently switch attention between multiple objects, reduced processing speed, a deficit in decision making ability, delayed reaction time, a deficit in the ability to anticipate or react to changes in the environment, lack of emotion control, and loss of consciousness or control.

Pending Legislation

There are more than a dozen bills pending in various state legislatures that may affect the way physicians address drowsy driving. These bills can be reviewed by clicking on the "public policy link" at www.drowsydriving.org. ■

Dr. Steven M. Brown, FCCP
Insomnia Center of Milwaukee
Milwaukee, WI

Drowsy Driving Prevention Week

NSF has declared November 5-11, 2007, Drowsy Driving Prevention Week.™ The campaign was launched to help save the lives of young drivers by raising awareness of the dangers of drowsy driving. In addition to teens, it will target other groups at high risk of drowsy driving, including commercial drivers, shift workers, and people with untreated sleep disorders. The campaign also aims to build a national grassroots network of advocates. According to NSF's 2006 *Sleep in America* poll, only one in five adolescents (20%) gets an optimal amount of sleep during the week, and more than half (51%) report having driven drowsy in the past year.

Where To Report Drowsy Drivers

Each state has its own regulations, laws, and mechanisms, whereby a physician may report an impaired driver, including drowsy drivers. States vary widely regarding (1) the duty of the physician to report impaired drivers, (2) the anonymity of the physician, (3) immunity, (4) legal protection, and (5) reporting procedures.

A very comprehensive guide was published by the American Medical Association with data as recent as May 2003. This 70-page document can be accessed at www.ama-assn.org/ama1/pub/upload/mm/433/chapter8.pdf. The Web site also contains contact information for obtaining updated local regulations.

AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

Chicago: Ready, Set, Go!

That's right, your trip to CHEST 2007 and the "Windy City" is right around the corner. We've already let you in on some of what Chicago has to offer, so here's a quick look at what's new at this year's annual meeting.

The keynote address on Monday, October 22, will feature guest speaker Jonathan Cohn, author of *Sick: The Untold Story of America's Health Care Crisis—and the People Who Pay the Price*. A veteran journalist, Mr. Cohn is the senior editor for *The New Republic* and a contributing editor for *The American Prospect*. He specializes in domestic politics and policy, with a primary focus on health care.

You'll enjoy a real hands-on experience when you visit a new ACCP exhibit at CHEST 2007. At The Pulmonary Office: A Blueprint for Innovation, you can experience the latest tools, techniques, and technologies to help you grow and manage your practice. In addition, you'll want to register online for a session in the ACCP Simulation Center, which offers nine separate sessions covering topics in shock management, airway management, ultrasonography, polysomnography, pulmonary function testing, disaster management in the ED, pediatrics, bronchoscopy, and health-care systems assessment. Hurry—space is limited! The ACCP also is giving you new tools to guide your education decisions and get organized today and in the future. The new ACCP Learning Categories, Maintenance of Licensure (MOL) subcategories, and online CME system are discussed in this issue of *CHEST Physician* on page 13.

If you haven't preregistered for the meeting, you can do so until October 5. After that time, on-site registration will be available at McCormick Place, Lakeside Center, our venue with a view.

Discover more things to see and do while you are in Chicago at www.choosechicago.com. Visit www.chestnet.org/CHEST for more information and details about CHEST 2007. ■

Last-Minute Checklist CHEST 2007

▶ **First and foremost—be there! October 20–25**
▶ **Bring your YELLOW registration packet with you** to the EXPRESS Check-in at McCormick Place, Lakeside Center
▶ **Don't miss Convocation and the Opening Reception** Sunday evening starting at 6:00 PM.
▶ **Plan to attend one or more NetWork meetings.**
▶ **Still time to register** for one or more of the excellent **postgraduate courses** being held on Saturday and Sunday.
▶ **Register online** at www.chestnet.org for a simulation session in the greatly expanded ACCP Simulation Center.
▶ **Don't miss the NEW ACCP exhibit**, The Pulmonary Office: A Blueprint for Innovation.
▶ **Reserve your seats for the Making a Difference Awards Dinner** at www.chestfoundation.org.

Schedule in these popular events—check your final program for times and locations:
▶ Daily literature review sessions
▶ Keynote session
▶ Curriculum-based learning sessions
▶ Poster grand rounds audio tours
▶ Practice management roundtable discussions
▶ CHEST Challenge Playoffs (Mon/Tues/Wed) and Championship (Wed evening)
▶ Walk/Run for Lung Health (Tues)
▶ Poster Best-in-Category Awards (Wed evening)

Free Food! Complimentary lunch will be served in the exhibit hall Mon-Wed. The satellite symposia offer complimentary breakfast or dinner before their events—choose from sessions on Mon and Tues mornings and evenings and Wed morning; Affiliate luncheon on Mon; Women's NetWork luncheon on Tues; and Cultural Diversity in Medicine luncheon on Wed.

Check the Ambassadors Group events listed in your final program.

Stop by ACCP Central! ACCP staff on hand to answer all your questions about the ACCP, The CHEST Foundation, NetWorks, and Institutes.

Shopping's always fun at the famous ACCP Bookstore. Featuring the newest ACCP-SEEK XVII—Pulmonary Medicine; 2007 Pulmonary, Critical Care, and Sleep Board Review syllabi; and more educational values and ACCP items.

Plus, **over 200 educational sessions** to optimize your CHEST 2007 experience.

Register today at www.chestnet.org. ■

NETWORKS

Transplant, Members in Industry, Respiratory Care

Transplant

For the potential lung transplant candidate, there is a bewildering amount of information to process in order to make an informed decision about whether to proceed with this emotionally and physically demanding procedure.

Physicians caring for a transplant candidate must be equally familiar with the risks and benefits of the procedure in order to effectively give counsel. Physicians must also be familiar with the seemingly vast array of potential complications and complexities of the immunosuppressive medications.

Members of the Transplant NetWork have been engaged in two important education projects to assist patients and caregivers with navigating the complex issues related to lung transplantation. The patient education guide, *A Guide to Lung Transplantation*, has been updated and posted on the Transplant NetWork Web page at www.chestnet.org/networks/transplant/index/php. This document provides a comprehensive description of the transplant process.

Another recently completed project is *The ACCP Guide to Lung Transplant Considerations for the Community Pulmonologist,* which also is available online. This guide provides community pulmonologists with recommendations on routine and preventive care for patients who receive transplants, as well as specific discussions of the clinical manifestations, diagnosis, and management of the protean complications that commonly arise.

Members in Industry

Physicians working in the pharmaceutical industry face increased scrutiny of their interactions with internal colleagues, health-care providers, and third-party payers. Previous changes in the regulatory environment had affected primarily the industry's promotion activities. Increasingly; however, industry physicians are the focus of external oversight, which has the potential to affect collaborative research, education efforts, and independent grant support.

Dr. Mark Forshag, FCCP, Regional Medical Research Scientist on the Infectious Diseases Team at Pfizer, will give the Members In Industry (MII) NetWork presentation at CHEST 2007, entitled, "Why Is the Enforcement Community Focusing on Clinical and Medical Affairs? How To Successfully Work With the Health-care Community in a Complex Compliance Environment." It will be held on Tuesday, October 23 at 8:30 AM in the Convention Center, E266.

A new activity for the NetWork at CHEST 2007 is "Career Conversations," a forum to learn about career opportunities in industry through discussions with MII Steering Committee representatives. The "Career Connections" table is in ACCP Central, with Steering Committee representatives available from 12:00 PM to 2:00 PM, Monday, October 22 through Wednesday, October 24.

For more information about this NetWork, go to www.chestnet.org/networks/accp_industry or e-mail networks@chestnet.org.

Respiratory Care

The NetWork invites all medical directors of respiratory care training programs to attend a special meeting at CHEST 2007. The meeting, scheduled for Monday, October 22, from 11:00 AM to 12:00 PM, will give these directors an opportunity to share concerns, problems, and knowledge. In addition, members of the Committee on Accreditation for Respiratory Care will attend to help answer questions and provide suggestions regarding the credentialing process and the role of the medical director.

This year's NetWork open meeting presenter is Dr. David Landsberg, FCCP. He will present "Utilizing Levalbuterol and Breath-Actuated Nebulizers to Optimize Respiratory Therapy Department Performance" on Wednesday, October 24, at 8:30 AM. Recent Respiratory Care NetWork projects include:
▶ Supporting the development of a Spanish version and a large print English version of the ACCP Inhaled Aerosol Device patient handouts. These handouts are available at www.chestnet.org/patients/guides/inhaledDevices.php.
▶ Advocating policies to government officials to ensure that civilian and military respiratory therapists undergo equivalent accredited education and credentialing.
▶ Reviewing existing ACCP position statements, including: Medical Director of Respiratory Care Department and Pulmonary Function Laboratory and Role of Respiratory Care Practitioners in the Delivery of Respiratory Care Services.
▶ Reviewing the utilization of respiratory therapists on medical emergency teams.

For more information about this NetWork, go to www.chestnet.org/networks/respiratory_care. ■

Deep Sedation in Intensive Care Worsened Risk of PTSD

BY ROBERT FINN
Elsevier Global Medical News

SAN FRANCISCO — A substantial proportion of patients experience posttraumatic stress disorder after their stay in an intensive care unit, and a new study has isolated three factors associated with an increased risk of developing the disorder, Christina Jones, Ph.D., reported at the International Conference of the American Thoracic Society.

In a prospective, observational study involving 238 patients from five ICUs in the United Kingdom, Sweden, Italy, and Norway, Dr. Jones of the University of Liverpool, England, and her colleagues found that 9.2% of the patients showed evidence of posttraumatic stress disorder (PTSD) 2 months following their discharge.

The factors independently associated with an increased risk of PTSD were deep sedation, physical restraint without sedation, and recall of delusional memories (Intensive Care Med. 2007;33:978-85).

In addition, a history of psychological problems indirectly predisposed patients to PTSD. Structural equation modeling showed patients with such a history were more likely to have delusional memories and to be sedated, and those two factors were in turn directly associated with PTSD.

The five ICUs were mixed, general, adult units. They were selected specifically because they had differing case mixes and different protocols reflecting the diversity of adult ICU practice across Europe. For example, different ICU units used different mixtures of sedative and opiate drugs at varying doses. And some ICU units used padded straps to restrain patients as an alternative to sedation.

Dr. Jones found it especially noteworthy that patients' delusional memories—not factual traumatic memories—were related to PTSD. Many delusional memories are based on actual events that the patients misinterpret. For example, a patient may interpret a simple injection as an attempted homicide. Such perceived losses of safety in the ICU make these memories particularly traumatic.

In conducting the study, the investigators prospectively recorded each patient's sedative and opiate drug type, duration, and dosage; the patient's level of sedation using the Motor Activity Assessment Scale; the presence and duration of delirium following sedation using the Confusion Assessment Method; the use and duration of physical restraint; and several other clinical and demographic parameters. All opiate and benzodiazepine doses were converted to morphine or lorazepam equivalents based on tables of relative potency.

Between 1 and 2 weeks after discharge from the ICU, investigators assessed the patients' recall using the ICU Memory Tool. Patients were asked about previous psychological problems, including anxiety and depression. Investigators excluded from the study all patients with preexisting or concomitant psychotic illness or those who had attempted suicide.

At 2 months following discharge, investigators administered the Posttraumatic Stress Syndrome 14–Question Inventory (PTSS-14). One month later investigators repeated the PTSS-14 and added the Posttraumatic Diagnostic Scale.

Dr. Jones said that further research is needed to understand whether the risk of PTSD can be reduced through changes within the ICU or whether it would be better to emphasize helping patients after ICU discharge. ■

Dr. Vera DePalo, FCCP, comments:
Increasing attention is being focused on the long-term outcome of critical illness. This study and others similarly attempt to determine how memories of intensive care treatment impact long-term quality of life. The study identifies that deep sedation, physical restraint without sedation, and recall of delusional memories are independently associated with an increased risk of PTSD. In a previous work (Crit. Care Med. 2001;29: 573-80), Dr. Jones and colleagues found that although delusional memories were associated with PTSD, factual memories seemed to be protective. Memory formation in the ICU is dependent on many factors, including the amount and quality of sleep. More research will be needed to identify optimum strategies that will help reduce the likelihood of PTSD and improve long-term quality of life following critical illness.

CLASSIFIEDS

PROFESSIONAL OPPORTUNITIES

BC/BE Intensivists

Prestigious pulmonary/critical care group practice seeking BC/BE intensivists for 24 hour/seven day a week in-house intensivist service for Chicago-area community hospital. This is a state-of-the-art facility in an attractive northwest suburb. We offer excellent compensation and benefits, including health and generous retirement programs, malpractice coverage and tail. Sorry, no J1 visas. For further information, please email CV and cover letter to sweissman@chestmd.com or fax to 773-935-2724.

Pulmonary and Critical Care Medicine

Pulmonary group in upstate South Carolina area that is completely physician owned and physician controlled has opportunity for candidate that is board certified/eligible in the area of pulmonary and critical care. Must be comfortable in both outpatient and inpatient settings. Practice offers a 1:4 call rotation and excellent growth potential. Fax cover letter and CV to 864-585-0999, Attn: Office Manager or
Email: cv.officemgr@yahoo.com

Pediatric Pulmonologist

Do you have an interest in helping patients with Cystic Fibrosis and a strong passion for children? We have a growing, academic pediatric department under new leadership that is seeking a team-oriented Pediatric Pulmonologist who enjoys teaching residents and medical students. You owe it to yourself to find out more information and see if you can qualify for this position at a prestigious academic medical center in one of the most desirable locations in the Midwest. For more information, please contact: Tolise Marie Steele, Account Executive, Adkisson Consultants, Toll Free: 866-781-1055, Fax: 309-452-7204, tolise@wefinddocs.com

Pulmonologist/Intensivist

Join our well-respected group of five Pulmonary/Critical Care/Sleep physicians in Billings, Montana. Collegial multispecialty group operates in up-to-date integrated hospital and clinic. Call is 1:6, shared with university trained, board certified specialists. Colleagues include strong surgical and medical sub-specialists, internists, family physicians as well as rapidly growing Hospitalist program. Near Absaroka/Beartooth Mountains and Yellowstone National Park. Family-centered and outdoor-oriented small city is the cultural and shopping center for the northern plains region. Our new associate will enjoy access to wilderness and practice tertiary care with many of the amenities but few of the hassles of a larger city. Contact: Rochelle Woods, 1-800-303-6893, physicianrecruiter@billingsclinic.org www.billingsclinic.com

Disclaimer

CHEST PHYSICIAN assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.

PHYSICIAN
TEXAS CENTER FOR INFECTIOUS DISEASES
SAN ANTONIO, TEXAS

The University of Texas Health Center at Tyler is seeking a highly motivated physician to join a subspecialty team practicing at a categorical tuberculosis inpatient facility in San Antonio, TX. Duties will be performed at the Texas Center for Infectious Diseases, a 75-bed inpatient facility specializing in the treatment of complicated tuberculosis patients. Must be board certified in Internal Medicine and BE/BC in either Pulmonary Medicine or Infectious Diseases. Competitive salary and generous benefit package. For further information, contact Robert Longfield, M.D., robert.longfield@dshs.state.tx.us 210-531-4597 or David Griffith, M.D., david.griffith@uthct.edu 903-877-7267. EOE

Carle Clinic Association

Carle Clinic Association, a 320-physician owned and operated multispecialty group practice, is seeking an additional BE/BC Pulmonology/Critical Care/Sleep Medicine physician to join an established department in Champaign-Urbana, Illinois. Practice includes office and hospital consultation, bronchoscopy, sleep disorders, intensive care, and pulmonary diagnostics. Position features the opportunity for academic and/or research affiliation with the University of Illinois. Champaign-Urbana has a population of 180,000 and is located two hours from Chicago and Indianapolis, and three hours from St. Louis. Please contact Dawn Goeddel at 800-436-3095, extension 4103 or via email at dawn.goeddel@carle.com

Pulmonary/Critical Care
Richmond, Virginia

Well-established group seeking BC/BE physician. 1:10 night call. 1:4 weekend daytime rounds. Considerable ICU nighttime coverage provided by EICU physician. Balanced call schedule spread amongst 20 FTE physicians. Practice includes Pulmonary, Critical Care, Sleep, Clinical Research, EICU. Sleep training great but not required. No grants to write. Teaching responsibilities not mandatory. Excellent base salary/benefits package with significant potential. No J-1 available. **Position available immediately and for 2008.** Contact Johnny Wong, MD. Send CV and cover letter to wongj@paraccess.com or FAX to 804-559-2357.

Marietta Pulmonary Medicine
Suburban Atlanta

Well-established, busy 12-physician single-specialty Pulmonary practice in suburban Atlanta, Georgia, looking for one or more BC/BE Pulmonary/Critical Care physicians. Sleep certification is a plus. Practice includes all aspects of pulmonary medicine, including critical care, sleep medicine, outpatient clinic, pulmonary rehab and clinical research. Practice located at one large acute-care hospital, with the busiest ER in Georgia, and also rounds at a nearby long term acute care hospital. Installation of an electronic ICU monitoring system planned for the near future. Competitive salary with bonus potential and generous benefits package. Fax CV to: 770-792-1738.

CLASSIFIED DEADLINES AND INFORMATION:
Contact: Rhonda Beamer, Walchli Tauber Group, Inc., 2225 Old Emmorton Road, Suite 201, Bel Air, MD 21015. (443) 512-8899 Ext 106. FAX: (443) 512-8909.
Email ad to: rhonda.beamer@wt-group.com

Sleep Apnea Treatment May Reduce Risk of Stroke

BY HEIDI SPLETE
Elsevier Global Medical News

MINNEAPOLIS — Sleep apnea, stroke, and sleep disorders are interrelated, Dr. Claudio Bassetti said at the annual meeting of the Associated Professional Sleep Societies.

Dr. Bassetti reviewed three areas in which studies support an association between sleep and stroke. Data suggest that sleep apnea is an independent risk factor for stroke, that sleep apnea and stroke are interrelated in cases of acute stroke, and that stroke-induced focal brain damage can promote hypersomnia and other sleep disorders.

Recognizing the relationship between sleep and stroke can help clinicians manage patients with sleep complaints who have other risk factors for stroke, and perhaps reduce the risk of stroke by treating sleep problems, said Dr. Bassetti, a neurologist at the University Hospital Zurich who specializes in sleep medicine.

Sleep Apnea and Stroke Risk

Studies of stroke and sleep-disordered breathing (SDB) done in the 1990s revealed that SDB was prevalent in patients who had suffered strokes. Recent studies that controlled for multiple risk factors support a possible link between SDB and stroke.

Dr. Bassetti cited an observational study of 1,022 adults, 698 of whom met the criteria for obstructive sleep apnea. In 6 years of follow-up, the individuals with obstructive sleep apnea were almost twice as likely to suffer strokes as were those who didn't have sleep apnea, even after controlling for age, gender, race, body mass index, alcohol and tobacco use, diabetes, hypertension, hyperlipidemia, and atrial fibrillation (N. Engl. J. Med. 2005;353:2034-41).

A clinical implication of these findings is that using continuous positive airway pressure (CPAP) devices might reduce stroke risk in patients with obstructive sleep apnea. A 10-year follow-up study of more than 1,600 adult men showed that patients with untreated severe obstructive sleep apnea/hypopnea were significantly more likely to have a fatal or nonfatal cardiovascular event than the following groups of men: patients treated with CPAP, untreated patients with mild or moderate sleep apnea, patients who snored, and healthy controls (Lancet 2005;365:1046-53).

Sleep Apnea's Role in Acute Stroke

About 50% of acute stroke patients will have obstructive sleep apnea, Dr. Bassetti said. His prospective study of 152 patients with acute ischemic stroke showed that SDB improved after the acute phase of stroke (Stroke 2006;37:967-72). But the presence of SDB predicted a greater risk of long-term mortality following a stroke. Clinicians can treat stroke patients with CPAP to reduce this risk, but compliance is a problem in patients with acute stroke, Dr. Bassetti explained.

"Unfortunately, there are no data suggesting which patients will tolerate CPAP," he said. But patients who can tolerate CPAP may reduce their risk of cardiovascular events following a stroke, he said.

Central sleep apnea, the rarer form of SDB in which in the brain fails to signal the respiratory muscles to breathe during sleep, also may be associated with acute stroke. Studies of stroke patients with central sleep apnea are rare, but central sleep apnea was recorded during 18%-24% of sleep in three patients who underwent polysomnographies after having first-time ischemic strokes. Breathing improved in all patients as they recovered from the strokes (Stroke 2007;38:1082-4).

Stroke as a Cause of Sleep Disorders

"Hypersomnia is very frequent in cases of stroke," Dr. Bassetti said. Hypersomnia can lead to attention and memory deficits in stroke patients. Be sure to ask about presleep behavior to help identify external causes of poststroke sleep problems, he said. Some patients recover or at least improve their symptoms with time, in part because hypersomnia is often caused by dysfunction of the arousal systems rather than by the stroke itself.

Insomnia rarely arises directly from a stroke, but focal brain damage has been associated with some cases of parasomnias, such as sleepwalking or night terrors, as well as with rare cases of neuropsychological dysfunction, Dr. Bassetti said.

He described one of his patients who developed Charcot-Wilbrand syndrome, which involves loss of the ability to dream as a result of focal brain damage. The patient, a 73-year-old woman, had a history of being able to dream and recall dreams, but she reported a total dream loss after an acute bilateral stroke. She showed no cognitive deficits and had normal REM sleep (Ann. Neurol. 2004;56:583-6). The case suggests that a stroke can affect sleep in distinct ways.

Stroke as a cause of sleep disorders is a potentially rich area of research, noted Dr. Bassetti. "I personally believe that sleep modulation may have an impact on stroke recovery," he said. ■

Opportunity...

CHEST 2007

October 20 - 25, 2007
Chicago, Illinois

For Clinical Education

- The world's largest-of-its-kind ACCP Simulation Center will feature 25,000 square feet of hands-on clinical experiences.
- Leading sessions will address new and breakthrough topics.
- Highly rated sessions will be back by demand.
- Exclusive look at original research will offer the first-ever review of new science.
- NEW! Special sessions will focus on emerging developments in chest medicine and practice management.

For Professional Growth

- NEW! The Pulmonary Office: A Blueprint for Innovation will showcase managing and building a practice.
- Renowned international faculty will be readily accessible for easy interaction.
- Original investigation presentations will offer opportunity to present your research.
- A large exhibit hall will showcase the latest technology advances.

Do Something
Uniquely Chicago
SINK your teeth into some deep-dish pizza at acclaimed restaurants.

AMERICAN COLLEGE OF CHEST PHYSICIANS
THE CHEST FOUNDATION™

Don't miss the opportunities.

For program details, visit
www.chestnet.org
(800) 343-2227 or (847) 498-1400

Sleep Apnea Impairs Drivers' Vigilance, Study Reveals

BY AMY ROTHMAN SCHONFELD
Elsevier Global Medical News

BOSTON — People with obstructive sleep apnea syndrome showed poorer vigilance while driving than did normal controls, a result that could not be predicted by pretest measures of disease severity or subjective reports of sleepiness, according to a poster presented by Dr. Jon Tippin at the annual meeting of the American Academy of Neurology.

Obstructive sleep apnea syndrome "can now be added to the list of diseases, including dementing illnesses like Alzheimer's disease and Parkinson's disease, that cause vigilance problems" during driving, said Dr. Tippin, a clinical professor of neurology at the University of Iowa, Iowa City.

Vigilance was assessed using the Simulator for Interdisciplinary Research in Ergonomics and Neuroscience (SIREN), an interactive driving simulator adapted from a car fitted with projection screens in front of and behind the driver.

OBSTRUCTIVE SLEEP APNEA SYNDROME SHOULD BE ADDED TO THE LIST OF CONDITIONS THAT COMPROMISE DRIVING CAPABILITY.

During simulations, drivers were asked to respond by clicking the high-beam control as soon as they detected light targets that were flashed at unpredictable temporal intervals (average one flash per minute) at seven locations across the forward horizon.

Hit rates and reaction times were the outcome measures. The hour-long test was administered in the late afternoon.

The overall hit rate was found to be lower in drivers with obstructive sleep apnea syndrome (OSAS) (n = 25) than in normal controls (n = 41) ($P = .018$). The data also suggested that people with OSAS were more likely to miss peripheral targets than those located in the central field of vision ($P = .0862$).

"These people do not have visual field impairments, but rather they show inattention to things in the peripheral field. As [drivers] becomes more inattentive, they focus more on the things right in front of them," Dr. Tippin said.

Although slower reaction times predicted poorer driving performance in all drivers (P less than .03), there was no difference in mean reaction times between the two groups.

People with OSAS were not sleepier than controls before the test, as indicated by the predrive Stanford Sleepiness Scale test. OSAS drivers were sleepier than controls at the end of the drive ($P = .027$), but only in OSAS drivers did the increased sleepiness correlate with poorer vigilance (as measured by lower hit rates, $P = .0135$).

Objective tests of sleepiness, such as polysomnography and the Multiple Sleep Latency Test done on the evening of and day after the drive, respectively, also did not correlate with vigilance or driving performance. "For patients with OSAS, the problem is less one of falling asleep than maintaining attention," Dr. Tippin said.

Factors such as age, obesity, and a sedentary lifestyle raise the risk for OSAS. For truck drivers, many of whom are known to have several of these risk factors, the likelihood of OSAS may be elevated to four times that of the general population, according to Dr. Tippin. In addition, sleep deprivation and fragmentation may compound the problem in this population.

Stakeholders such as the Federal Motor Carrier Safety Administration (FMCSA), the trucking industry, and insurance carriers are working to develop guidelines regarding illness and driving, Dr. Tippin noted.

He suggested that obstructive sleep apnea syndrome should be added to the list of conditions that compromise driving capability. ■

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CSL Behring
Zemaira®
Alpha$_1$-Proteinase Inhibitor (Human)

Manufactured by:
CSL Behring LLC
Kankakee, IL 60901 USA
US License No. 1767

℞ **only**

Before prescribing, please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE
Zemaira® is indicated for chronic augmentation and maintenance therapy in individuals with alpha$_1$-proteinase inhibitor (A_1-PI) deficiency and clinical evidence of emphysema.
Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A_1-PI.
Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.
Safety and effectiveness in pediatric patients have not been established.
Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A_1-PI deficiency has not been established.

CONTRAINDICATIONS
Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A_1-PI products.
Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

WARNINGS
Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See **DESCRIPTION** section for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.
Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).
During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

PRECAUTIONS
General - Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.
As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.
Information For Patients - Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.
As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.
Pregnancy Category C - Animal reproduction studies have not been conducted with Zemaira®, Alpha$_1$-Proteinase Inhibitor (Human). It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.
Nursing Mothers - It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.
Pediatric Use - Safety and effectiveness in the pediatric population have not been established.
Geriatric Use - Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS
Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated. In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild.
Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.
Table 3 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prolastin®. No clinically significant differences were detected between the two treatment groups.

Table 3: Summary of Adverse Events

	Zemaira®	Prolastin®
No. of subjects treated	89	32
No. of subjects with adverse events regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).
The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia.
Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.
In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prolastin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

HOW SUPPLIED
Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A_1-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one vented transfer device.

STORAGE
When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

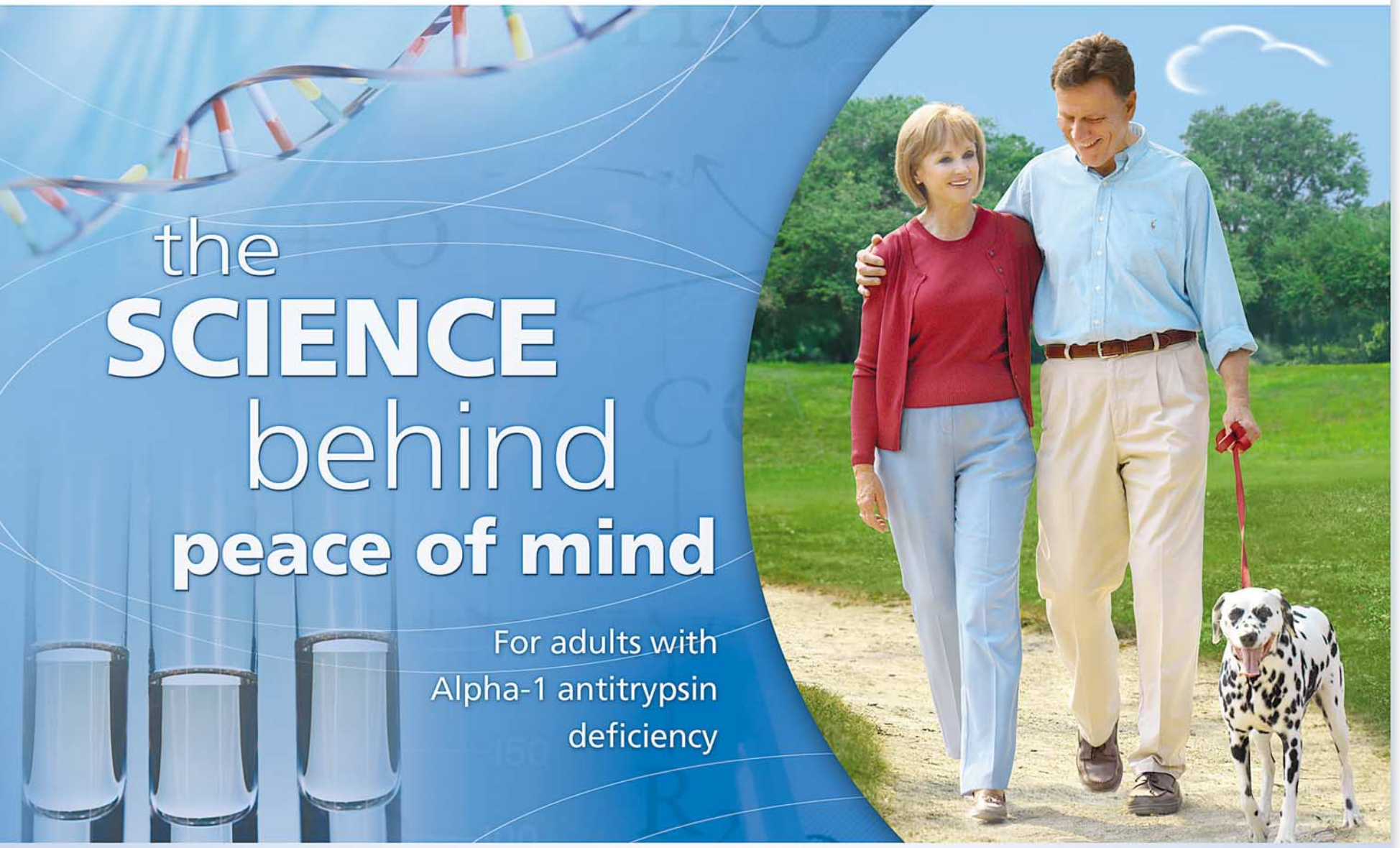
Prolastin® is a registered trademark of Bayer Corporation.

Revised: January, 2007 Adapted from 19131-05

© 2007 **CSL Behring LLC** • 1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901, USA • www.CSLBehring-US.com IO#8Z008 8/2007

INDEX OF ADVERTISERS

CSL Behring



Zemaira® — The next generation in purity for Alpha-1 augmentation therapy

- **Pure** — The only Alpha-1 augmentation therapy approved by the FDA as highly purified (lot release specification, ≥94% purity)*,[1-3]
- **Effective** — **Three times fewer** COPD exacerbations than with Prolastin®†
- **Well tolerated** — **Six times fewer** infusion-related adverse events than with Prolastin®‡
- **Fast** — **Half or less** the infusion time of other augmentation therapies§,[1-3]

Zemaira® is indicated for chronic augmentation and maintenance therapy for adults with alpha$_1$-proteinase inhibitor (A_1-PI) deficiency and emphysema.

Clinical data demonstrating the long-term effects of chronic augmentation therapy with Zemaira® are not available.

As with other Alpha-1 therapies, Zemaira® may not be appropriate for the following adult individuals as they may experience severe reactions, including anaphylaxis: individuals with a known hypersensitivity and/or history of anaphylaxis or severe systemic reaction to A_1-PI products or their components and individuals with selective IgA deficiencies who have known antibodies against IgA.

In clinical studies, the following treatment-related adverse events were reported in 1% of subjects: asthenia, injection-site pain, dizziness, headache, paresthesia, and pruritus.

Zemaira® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

For more information, call **1-866-ZEMAIRA (1-866-936-2472),** or visit **www.Zemaira.com.**

References: 1. Prolastin® Alpha$_1$-Proteinase Inhibitor (Human), Full Prescribing Information, January 2005. **2.** Aralast™ Alpha$_1$-Proteinase Inhibitor (Human), Full Prescribing Information, August 2005. **3.** Data on file, CSL Behring LLC.

Zemaira®
alpha$_1$-proteinase inhibitor (Human)
Unmatched purity. Uncompromised care.

Please see brief summary of full prescribing information on following page.

* Shelf life purity specification is ≥90%

† In a retrospective analysis in the pivotal clinical trial, Zemaira® patients were three times less likely to experience exacerbations of their COPD than Prolastin® patients

‡ No clinically significant differences were detected between the treatment groups

§ Based on recommended dosage as stated in the product package inserts of 60 mg/kg body weight at the infusion rate of 0.08 mL/kg/min

Prolastin is a registered trademark of Talecris Biotherapeutics, Inc.