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The ExPress Study results may suggest a trend for better survival rates in a ventilation strategy aimed at improving lung recruitment.

Higher PEEP May Mean Better Outcomes

BY MICHELE G. SULLIVAN

Elsevier Global Medical News

BARCELONA — Ventilation strategies aimed at opening the lung with higher positive end-expiratory pressure settings appear safe and may decrease both short- and longer-term mortality in patients with acute lung injury, investigators said at the annual congress of the European Society of Intensive Care Medicine.

Preliminary analyses of two very recently completed European ventilation trials also concluded that these strategies were associated with lower rates of rescue therapies, and didn't significantly increase the rate of barotrauma in ventilated patients.

Dr. Alain Mercat, of the University Hospital of Angers, France, presented the results of the ExPress (Expiratory Pressure) study. The randomized controlled trial examined 28- and 60-day mortality in 767 acute respiratory distress syndrome patients.

Patients were randomized to ventilation using one of two end-expiratory pressure (PEEP) strategies: minimal alveolar distention (total PEEP set between 5 and 9 cm/H₂O) or maximal alveolar recruitment (PEEP set to obtain a plateau pressure of 28-30 cm/H₂O). Both strategies used a target tidal volume of 6 ml/kg of predicted body weight.

The patients' mean age was 60 years. Their mean SAPS II score

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TORCH Brightens Patients' COPD Survival Prospects

'This study brings a message of hope.'

BY BRUCE JANCIN

Elsevier Global Medical News

SALT LAKE CITY — The combination of inhaled salmeterol and fluticasone propionate is the first-ever drug therapy shown to reduce mortality in patients with chronic obstructive pulmonary disease, according to the results of the landmark Towards a Revolution in COPD Health (TORCH) study.

The findings, presented by Dr. Bartolome R. Celli, FCCP, at the annual meeting of the American College of Chest Physicians, offer hope to patients with COPD—a seriously underdiagnosed disease and the fourth-leading cause of death.

"This study brings a message of hope," declared Dr. Celli in presenting the findings. "Not only did it show that patients with COPD live longer with the combination of salmeterol and fluticasone, but they do so with fewer exacerbations and a better quality of life. Now we can add to oxygen therapy and smoking

cessation another type of therapy that impacts mortality."

TORCH was a 3-year, double-blind, four-arm clinical trial involving 6,112 patients with moderate to severe COPD. They were randomized to b.i.d. placebo, the long-acting bronchodilator salmeterol at 50 mcg, the corticosteroid fluticasone propionate at 500 mcg, or fluticasone/salmeterol 500/50 mcg. The combined therapy is marketed as Advair in the United States, Viani in Germany, and Seretide elsewhere.

The primary end point was all-cause mortality. After 3 years, mortality was 12.6% with fluticasone/salmeterol and 15.2% with placebo, for a 17% relative risk reduction. COPD-related mortality was reduced by 22%; the rates were 4.7% with combination therapy and 6.0% with placebo. Neither salmeterol nor fluticasone alone was significantly better than placebo.

The combination therapy

See TORCH • page 2

Lung Cancer Screening May Boost Survival

BY JOHN R. BELL

Elsevier Global Medical News

CT screening of asymptomatic patients at risk for lung cancer may boost survival rates for those with stage I cancer and prove to be cost-effective, according to the results of a multicenter observational study.

The early screening initiative led to estimated 10-year survival rates of 92% in patients with detected stage I lung cancer who underwent resection within a month of diagnosis, the study's authors reported.

"In a population at risk for lung cancer, such screening could prevent some 80% of deaths from lung cancer," wrote investigators from the International Early Lung Cancer Action Program. In addition, "we found CT screening

for lung cancer to be highly cost-effective."

The program, led by Dr. Claudia Henschke of Cornell University, New York, and comprising I-ELCAP sites in the United States, Canada, Japan, China, Israel, Italy, and Spain, reported results for a group of 31,567 asymptomatic but at-risk patients (median age 61 years) screened between 1993 and 2005 (N. Engl. J. Med. 2006;355:

1763-71). Of this cohort, 412 were diagnosed with stage I lung cancer.

All participants underwent a baseline CT screening. Those with negative results subsequently underwent annual spiral CT screenings.

Patients who at baseline had a positive result (at least one solid or partially solid noncalcified

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VITAL SIGNS

Median Income of Chest Physicians in Group Practice Up 47% Over the Past Decade



Source: American Medical Group Association

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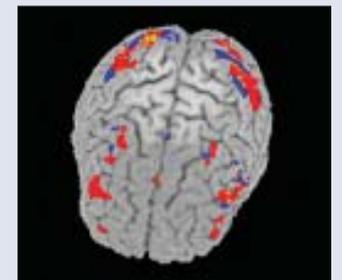
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COPD Exacerbations Cut 25%

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performed significantly better on all secondary end points as well. The incidence of moderate to severe exacerbations was reduced by 25% compared with placebo. Health status as measured by the St. George's Respiratory Questionnaire was better than with either drug alone or placebo. And mean forced expiratory volume in 1 second (FEV₁) was 91 mm Hg higher in the fluticasone/salmeterol arm than with placebo, added Dr. Celli, professor of medicine at Tufts University, Boston.

Nonfatal pneumonia, hoarseness, and oral thrush were significantly more common with combination therapy. But there was no increase in cataracts, nontraumatic fractures, or loss of bone mineral density at the hip compared with placebo.

TORCH was the largest clinical trial in COPD. Given the size of the study, Dr. Celli said, "to me the signal is strong enough to say that given the inclusion criteria of the study—an FEV₁ below 60% of predicted, more than 10 years of smoking, obstruction by spirometry, and no asthma—that person should benefit from the combination."

"TORCH is clearly one of the most important studies in respiratory medicine in

a very long time," said Dr. Ronald F. Grossman, FCCP, who was not involved in the trial. He shrugged off the borderline significance of the all-cause mortality reduction, $P = .052$, by intention-to-treat analysis. "Most of the dropouts in the placebo arm occurred in the first year. A good proportion of them were probably on effective therapy for much of the 3 years, yet they were counted in the placebo group. So if anything, the mortality effect is a very, very conservative estimate," said Dr. Grossman, professor of medicine at the University of Toronto.

Advair is currently Food and Drug Administration–indicated only at a 250/50 mcg formulation. The 500/50 mcg formulation is marketed outside the United States. The company plans to seek FDA approval of the 500/50 mcg formulation.

Dr. Celli is a consultant to GlaxoSmithKline, which funded TORCH. ■

Dr. Mark Dransfield comments: *The statistical significance of the primary outcome of the TORCH study will be debated, but several other considerations deserve mention. First, in addition to the issue of differential dropouts mentioned by Dr. Grossman, it is important to note that overall mortality in the placebo arm was lower than had been predicted during study planning. This reduced the power of the study to detect a mortality benefit. Second, when analyzed using Cox proportional hazards testing adjusting for baseline FEV₁ and smoking status, survival was better with combination therapy (hazard ratio 0.811; $P = 0.031$). Of particular note given the controversy regarding the safety of long-acting beta-2 agonists, there was no difference in mortality between the salmeterol and placebo arms of the study, arguing that the drug is safe in this population of COPD patients.*

(Disclosure: Dr. Dransfield has received grant funding from GlaxoSmithKline and is a member of its speakers bureau.)

Higher PEEP Shows Promise

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was 15; 60% had septic shock, and the mean PaO₂/FiO₂ ratio was 140. Weanability trials began at day 4, according to patients' individual progress.

After 4 days, the mean PEEP setting was 14 in the maximal group and 7 in the minimal group. The mean PEEP plateau pressure was 28 cm/H₂O in the maximal group and 21 cm/H₂O in the minimal group.

There was significantly more fluid loading in the maximal group (1.5 liters vs. 1.1 liter), but significantly fewer patients in the maximal group needed the prone position for lung recruitment (9% vs. 19%), or inhaled nitrous oxide (19% vs. 26%).

Pneumothorax was uncommon and not different between the groups (7% vs. 6%). The number of ventilation-free days was slightly, but significantly, higher in the maximal group (9.5 vs. 8).

There was a nonsignificant decrease in mortality at day 28 (28% vs. 31%), and at day 60 (36% vs. 39.5%).

The results "suggest a trend for better outcomes in a ventilation strategy aimed at improving lung recruitment," Dr. Mercat said. The next step will be to initiate studies aimed at better identification of recruiters and nonrecruiters, so that PEEP settings can be optimally managed, he added.

Dr. Thomas Stewart and Dr. Maureen Meade, both of McMaster University, Hamilton, Ont., presented an early analysis of the Lung-Open Ventilation Strategy in Acute Lung Injury study, funded by the Canadian government and carried out in Canada and Australia.

The 983 patients in this randomized controlled trial all had acute lung injury with a PaO₂/FiO₂ ratio that was less than 250.

The control therapy consisted of a targeted tidal volume of 6 ml/kg of predicted body weight (range 3-8 ml/kg)

and a PEEP plateau pressure of 30 cm/H₂O. The lung open ventilation (LOV) strategy consisted of the same mean tidal volume, with a PEEP plateau of 40 cm/H₂O. Lung recruitment maneuvers were also allowed in the LOV group.

The patients' mean age was 56 years, with those in the control group being slightly, but not significantly, older. Their mean APACHE II score was 25.5 and the mean PaO₂/FiO₂ ratio was 142.

Almost half of the group (46%) had sepsis; there were slightly more sepsis patients in the control group, which could have portended a worse outcome, said Dr. Meade.

The separation of PEEP levels was highest during the first 3 days, when the average difference between groups was 4.5 cm/H₂O.

In-hospital mortality was significantly higher in the control group than in the LOV group (40% vs. 36%), for a risk ratio of 0.90.

When adjusted for age and the presence of sepsis, the mortality difference was not significantly different, but was still higher in the control group (39% vs. 38%).

LOV patients had significantly less refractory hypoxemia (5% vs. 10%). The LOV group also had a modest, but nonsignificant, decrease in refractory acidosis (6% vs. 8%), and a nonsignificant increase in barotrauma (3% vs. 2%).

The use of rescue therapies was relatively low but significantly more common in the control group control (12% vs. 8%).

"The context of these findings is key," Dr. Meade said. "They are consistent with those of other trials comparing current ventilation strategies, including ExPress and the adjusted analysis of the ALVEOLI trial (N. Engl. J. Med. 2004;351:327-36)." ■

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CT Study Is a 'Welcome Salvo'

Lung Cancer Screening • from page 1

nodule at least 5 mm in diameter, one or more nonsolid noncalcified pulmonary nodules 8 mm or larger, or a solid endobronchial nodule) received another CT scan 3 months later or an immediate PET scan followed by fine-needle-aspiration (FNA) biopsy for PET-positive lesions or 3-month follow-up CT for PET-negative lesions. Nodules 15 mm or larger at baseline could also undergo immediate biopsy. Signs of nodule growth seen in the 3-month scans prompted FNA biopsy,

whereas work-up ceased for lesions with no growth.

A total of 484 patients were diagnosed with lung cancer. Of those, 405 were diagnosed at baseline, and annual CT examination found another 74 patients with lung cancer; 5 additional patients were diagnosed with lung cancer between baseline and 12 months. Of the patients with lung cancer, 412 had disease at stage I.

The investigators conducted a Kaplan-Meier survival analysis of the cohort and

found an estimated 10-year survival rate of 88% in the stage I group. The estimated 10-year survival rate was 92% among the 302 patients whose lung cancer was resected within 1 month of diagnosis. Notably, all eight patients who refused treatment for their cancer died within 5 years of diagnosis.

Cost-effectiveness estimates of CT screening for lung cancer are similar to those of mammography screening, the investigators noted. The cost of low-dose CT is less than \$200, they wrote, and surgery to remove stage I lung cancer is less than half the cost of treatment in late-stage lung cancer.

In asymptomatic people, "the serendipitous discovery of lung cancer ... is currently the principal way in which stage I lung cancer is detected," Dr. Michael Unger of Fox Chase Cancer Center, Philadelphia, noted in an accompanying editorial (*N. Engl. J. Med.* 2006;355:1822-4). The historically low survival rate for patients with lung cancer is partly due to the advanced disease stage at the time most lung cancers are diagnosed, he added.

In the study, the high cure rate in patients whose disease was promptly resected "was similar to the rate among patients with early-stage breast cancer that is detected by means of mammography and ultrasound," Dr. Unger wrote.

Important questions remain unanswered, however. Biases such as overdiagnosis and lead time could have found their way into the mortality analysis, Dr. Unger cautioned, and chest CT scans on their own don't reveal differences between growing granulomatous lesions and tumors. Despite the investigators' assertions, "the question of cost-effectiveness remains unanswered," he added.

Nonetheless, Dr. Unger concluded, the study "is a provocative, welcome salvo in the long struggle to reduce the tremendous burden of lung cancer on society."

Dr. W. Michael Alberts, FCCP, comments:

This study provides additional evidence that CT screening MAY convey a survival advantage. We all have high hopes that the randomized controlled trials of CT screening currently underway will allow us to better answer the question.

Workers' Respiratory Symptoms Improve After Smoking Ban

Banning smoking in public places improves the signs and symptoms of smoking-related illness in bar workers, according to Dr. Daniel Menzies of the Asthma and Allergy Research Group at Ninewells Hospital in Dundee, Scotland.

"The recent introduction of legislation in Scotland prohibiting smoking in enclosed public spaces has led to a rapid and marked improvement in the health of bar workers," Dr. Menzies and his colleagues reported (*JAMA* 2006;296:1742-48).

The researchers conducted a prospective study of 77 bar workers, none of whom were active smokers at the time of the study, in a Scottish city from February to June 2006. The ban on smoking in enclosed public spaces went into effect March 26, 2006.

The results showed statistically significant changes in many pre- and postban measures. The percentage of bar workers with respiratory and sensory symptoms fell from 79.2% before the ban to 46.8% 1-2 months later. Forced expiratory volume in the first second rose from 96.6% predicted to 104.8% predicted, and serum cotinine levels decreased from 5.15 ng/mL to 3.22 ng/mL. Airway inflammation also decreased, as shown by a reduction in exhaled nitric oxide from 34.3 parts/billion to 27.4 parts/billion 1 month after the smoking ban went into effect.

—Sarah Pressman Lovinger

CHANTIX™
(varenicline) TABLETS



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 fibroma (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 benefits justify 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.

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.

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 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
RESPIRATORY/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	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, of 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 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. **HEPATOBIILIARY 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:** Bradypnea, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS. Frequent:** Polyuria. **Infrequent:** Nephrolithiasis, Nocturia, Urine abnormally, Urinary 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 2006, Version LAB-0327-2.0

FDA Approves Bevacizumab in Lung Cancer Regimen

BY ELIZABETH MEHCATIE
Elsevier Global Medical News

The Food and Drug Administration last month gave physicians a new tool in the battle against lung cancer, approving the antiangiogenesis agent bevacizumab in combination with chemotherapy as an initial treatment of unresectable non-small cell lung cancer.

"While this is not a silver bullet or panacea, this is an incremental benefit and represents a significant advance in treatment," said Dr. W. Michael Alberts, FCCP, chief medical officer at the H. Lee Moffitt Cancer Center, Tampa, and past president of the American College of Chest Physicians.

The FDA okayed the combination of bevacizumab, a recombinant monoclonal antibody that inhibits angiogenesis,

and carboplatin and paclitaxel as initial systemic treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous non-small cell lung cancer.

The FDA approval was based on a study of more than 800 patients and demonstrated that adding bevacizumab to the standard chemotherapy regimen increased mean survival by about 2 months, according to the FDA.

Bevacizumab, marketed as Avastin by Genentech, is a therapeutic antibody that binds to and inhibits human vascular endothelial growth factor (VEGF), thought to play a role in angiogenesis and maintenance of blood vessels in tumors, according to Genentech.

The randomized, controlled, multicenter trial enrolled 878 patients with unresectable, locally advanced, recurrent or metastatic nonsquamous NSCLC

who had not been treated with chemotherapy previously. Median patient age was 63 years.

All patients were treated with carboplatin and paclitaxel; about half also received bevacizumab, administered in an intravenous infusion every 3 weeks.

The median overall survival for patients receiving bevacizumab was 12.3 months, vs. 10.3 months among those who did not receive bevacizumab.

One-year survival was 51% among those on bevacizumab and chemotherapy, vs. 44% among those patients on chemotherapy alone, according to Genentech.

This was a median increase, so survival in some patients was greater than 2 months, commented Dr. Alberts. Some patients in the trial were from his institution, but Dr. Alberts said he has no financial ties to Genentech.

The trial was conducted by a network of investigators led by the Eastern Cooperative Oncology Groups and was sponsored by the National Cancer Institute, according to the company.

Neutropenia, fatigue, hypertension, infection, and hemorrhage were the most common severe adverse events in bevacizumab-treated patients.

In the study, 2.3% of those patients in the bevacizumab arm had pulmonary hemorrhage requiring medical intervention, vs. 0.5% among those on chemotherapy alone.

Pulmonary hemorrhage was fatal in seven patients in the bevacizumab arm and one in the chemotherapy-only arm.

Genentech plans to launch a program in January that will cap the cost of bevacizumab therapy at \$55,000 a year for eligible patients for any FDA-approved use of bevacizumab. ■

POINT/COUNTERPOINT

Should Inflammatory Markers Be the Basis of Monitoring Asthma?

Yes

Asthma is a chronic inflammatory disease. We know that the severity of asthma corresponds to the severity of inflammation, and that inflammation is treatable. Treatment algorithms that include measures of inflammation improve outcomes. So it makes sense that inflammatory markers should be the basis of monitoring asthma.

Studies of asthma exacerbations have detected a range of markers, including sputum eosinophils, peripheral blood eosinophils, serum eosinophil cationic protein, cytokines, 8-isoprostane, and leukotrienes. All have methodologic issues that can limit their use, particularly in young children. In steroid-withdrawal studies, their sensitivity and specificity have been about 50% for predicting an exacerbation.

An archetypal study by Sont and colleagues evaluated adults with mild to moderate asthma. The corticosteroid dose was adjusted either in a stepwise progression or in a stepwise progression plus airway responsiveness measurements. The more intensively managed group had the same number of exacerbations over the 2-year period as those without airway responsiveness, and clearly many fewer exacerbations than those who had airway responsiveness but weren't on the intensive protocol. Also, the managed arm had improved histology but a 400-mcg rise in daily inhaled steroid use.

Measurements of the fraction of exhaled nitric oxide (Fe_{NO}), induced sputum, and exhaled breath condensate are the most studied techniques, with more than 200 articles published on exhaled nitric oxide alone in the past 12 months. Two well-publicized studies used a rationale similar to that used by Sont and colleagues.

In contrast, a 2005 study by Smith et al. in adults with chronic asthma showed no change in exacerbations or in inflammation as determined by sputum eosinophils

in patients whose corticosteroid dose was adjusted in a stepwise fashion on the basis of either exhaled nitric oxide (eNO) measurements or an algorithm based on conventional guidelines. But patients in the eNO arm used a lower mean dose of inhaled corticosteroids (*N. Engl. J. Med.* 2005;352:2163-73).

Perhaps more relevant to those treating children is the 2005 study by Pijnenburg et al. that reported a reduction in corticosteroid use in children whose steroids were managed on the basis of eNO evaluations, compared with those managed conventionally. There were no differences between the two arms in clinical outcomes, but the authors reported a significant improvement in airway responsiveness to methacholine in the eNO arm. The children in this group were more responsive at baseline, suggesting that this finding reflects a regression to the mean (*Am. J. Respir. Crit. Care Med.* 2005;172:831-6).

Measurement of exhaled breath condensate is simple and has the advantage of detecting a range of substances. The method may be a desirable option in children, with more than 90% of children completing the measurement in some studies. But there are data showing that the sensitivity of exhaled breath condensate is lower than that of induced sputum.

Although we don't have the best tests available at the moment to measure airway inflammation, and because there is overwhelming evidence that asthma is an inflammatory disorder, we should aim to develop appropriate tools and test them using relevant clinical algorithms. ■

STEPHEN STICK, M.D., is a clinical associate professor in the School of Pediatrics and Child Health, University of Western Australia, and head of the respiratory medicine department at the Princess Margaret Hospital for Children, Perth, Australia.

No

In addition to history taking and clinical examination, various techniques have been developed recently that are thought to reflect asthmatic inflammation, such as the concentration of nitric oxide in exhaled breath, the cellular characteristics of induced sputum, and the composition of condensates of exhaled breath. At present, there is no evidence that these methods are of great value in monitoring or controlling asthma.

Numerous nitric oxide studies were published last year, including three important studies that purport to support the use of exhaled nitric oxide (eNO) for monitoring asthma.

The first, published in May 2005 in the *New England Journal of Medicine* (352:2163-73), reported a moderate reduction in inhaled corticosteroid use and a nonsignificant reduction in the rate of exacerbations in adult asthmatics using eNO, compared with those monitored by conventional means.

There was no significant reduction in other markers of asthma control or levels of inflammation and no mention of the cost of multiple eNO measurements.

The results of the two other studies in children were more impressive. In a study by Pijnenburg et al., there was an improvement in bronchial reactivity in the children managed with eNO, but no real difference in their clinical condition. In addition, the difference in bronchial hyperresponsiveness was just 1.3 doubling doses between controls and eNO-managed children, which is clinically meaningless.

A study by Zacharasiewicz et al. demonstrated that an elevation of eNO during steroid reduction predicted an exacerbation, but the best sensitivity and specificity values for the test were only 70%-80% (*Am. J. Respir. Crit. Care Med.* 2005;171:1077-82).

Others have suggested that induced

sputum eosinophils are the best way to estimate the severity of airway inflammation in asthma. Expecterated sputum is induced by the inhalation of hypertonic saline, which requires considerable cooperation from the patient. In three studies that I looked at, satisfactory sputum samples were collected in some 60%-76% of older children, aged 10-12 years. As we all know, many of the patients we treat for asthma are younger than this.

As to whether sputum analysis is useful, the results are mixed. In the study by Zacharasiewicz et al., a sputum eosinophilia of over 2% had only about 60%-70% sensitivity and specificity for predicting an asthma exacerbation. In a study by Wilson et al. in which they were able to collect sputum in 60% of children, there was no correlation between sputum eosinophilia and clinical asthma (*Thorax* 2000;55:768-74).

The results have been more encouraging in adults, including a study by Green et al. that showed management based on induced sputum could produce fewer exacerbations, even though it did nothing to improve lung function or alter corticosteroid use (*Lancet* 2002;360:1715-21).

I suggest that the best use for eNO is to differentiate asthma from other types of obstructive lung diseases such as cystic fibrosis and primary dyskinesia.

Equally, consistently high nitric oxide levels in a child who is supposed to be on corticosteroids can tell us that the child is quite likely not taking his or her steroids.

Based on the current evidence, the one thing we can agree on is that further study will show the practical ability of including these measurement tests in clinical practice. ■

SIMON GODFREY, M.D., is a professor in the Institute of Pulmonology, Hadassah University Hospital, Jerusalem.

Oxygen Therapy May Not Always Live Up to Its Billing

BY HEIDI SPLETE
Elsevier Global Medical News

CHARLESTON, W.VA. — Supplemental oxygen might help many more patients with chronic obstructive pulmonary disease during exercise, sleep, and airplane flights—but then again, it might not, Dr. Richard Casaburi, FCCP, said at the annual meeting of the American Association of Cardiovascular and Pulmonary Rehabilitation.

Although recent evidence-based guidelines for managing COPD patients with chronic low oxygen levels include long-term oxygen therapy, the benefits of using supplemental oxygen in certain situations remain unclear.

“Oxygen is a great therapy, but are we sure that we’re not using it in too many patients?” Dr. Casaburi said. “In some cases, we give people oxygen without evaluating them as fully as we might.”

The physiologic benefits of supplemental oxygen are understood: It promotes oxygen supply to the body’s tissues and inhibits activity of the carotid body, which monitors blood oxygen levels, explained Dr. Casaburi, professor in the division of respiratory and critical care physiology and medicine at the University of California, Los Angeles.

Current evidence supports arguments both for and against supplemental oxygen for COPD patients in certain circumstances. Dr. Casaburi presented his own pro and con debate at the meeting. He has received grants from and served as a consultant for Boehringer-Ingelheim GmbH, Novartis AG, Inogen, Altana AG, Pfizer Inc., and GlaxoSmithKline.

Oxygen During Exercise

Evidence from several studies shows that when COPD patients receive supplemental oxygen during exercise, they experience less breathlessness, more controlled breathing, and decreased overinflation of the lungs.

Supplemental oxygen also allows patients to exercise longer and promotes exercise tolerance by increasing the oxygen supply to the exercising muscles. These benefits occur even in patients without clinically significant hypoxemia, Dr. Casaburi said. He cited a randomized, single-blinded, controlled study in which COPD patients who received oxygen while exercising more than doubled their endurance time during a stationary cycling test compared with breathing compressed air (*Eur. Respir. J.* 2001;18:77-84).

On the other hand, no investigations

have conclusively shown better long-term outcomes for COPD patients who receive supplemental ambulatory oxygen. Further, it seems possible that many patients who currently receive ambulatory oxygen don’t use it for a long enough period each day to generate long-term benefits, Dr. Casaburi said.

Oxygen During Air Travel

Most commercial flights are pressurized to approximately 8,000 feet, and many COPD patients become hypoxemic at that altitude, Dr. Casaburi said. In theory, all COPD patients with severe disease could be evaluated with an altitude simulation test before flying to determine their need for supplemental oxygen.

On the other hand, supplemental oxygen use during an airplane flight is awkward and expensive, and studies have shown that most COPD patients can tolerate moderate hypoxemia while flying.

Oxygen During Sleep

Nighttime oxygen therapy may be helpful for some patients with severe COPD whose hypoxemia is worse during sleep, according to the current guidelines from the American Thoracic Society and the European Respiratory Society.

COPD patients who have a daytime arterial oxygen pressure (PaO₂) greater than 60 mm Hg with proven nighttime oxygen desaturation showed improved pulmonary artery pressure when they received supplemental oxygen at night for 36 months in a randomized study of 51 patients (*Am. Rev. Respir. Dis.* 1992;145:1070-6).

On the other hand, no research has shown improved long-term survival when COPD patients with isolated incidents of

nighttime oxygen desaturation receive supplemental oxygen while sleeping, Dr. Casaburi said. A randomized study of 76 patients contradicted the 1992 study and showed no improvement in pulmonary artery pressure among those who received nighttime oxygen compared with those who did not (*Eur. Respir. J.* 1999;14:1002-8).



‘Oxygen is a great therapy, but are we sure that we’re not using it in too many patients?’

DR. CASABURI

What’s Next?

Two distinct studies are needed to help clinicians put the issue of ambulatory oxygen use for COPD patients on firm scientific ground, Dr. Casaburi concluded.

First, a study should compare the impact of stationary oxygen plus ambulatory oxygen vs. stationary oxygen alone on the long-term well-being of COPD patients who are hypoxemic both at rest and during exercise. Second, a study should compare ambulatory oxygen vs. no oxygen for patients

whose oxygenation is normal at rest but who desaturate with exercise.

Large-scale studies are needed because the stakes are high for COPD patients. Such studies are difficult to conduct but worthwhile, Dr. Casaburi said.

To assess the survival outcomes of long-term oxygen therapy in COPD patients who do not meet current criteria for long-term oxygen use but have a poor prognosis, a large-scale study is being planned. The National Institutes of Health are reviewing applications, and the study will potentially include 5,000 patients from 20 sites in the United States.

Patients will be randomized to receive usual care or usual care plus long-term oxygen therapy (both stationary and ambulatory). Final details of the study design will be determined by the investigators from the individual sites. ■

November Is COPD Awareness Month Lung Cancer Awareness Month

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World COPD Day is November 15



November 16 is the Great American Smokeout

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www.chestnet.org/copd
www.chestnet.org/lungcancer



Nebulized Arformoterol Solution Approved for COPD Treatment

A nebulized formulation of a new long-acting β_2 -agonist has been approved by the Food and Drug Administration for treatment of chronic obstructive pulmonary disease.

Arformoterol tartrate was approved in early October for the long-term maintenance control of bronchoconstriction in people with COPD. The recommended dose is 15 mcg administered twice a day, in the morning and evening.

Arformoterol is supplied in a 15 mcg/2 mL solution. It is marketed by Sepracor under the trade name Brovana, and as an inhalation powder formulation under the name Foradil. Arformoterol is twice as potent as racemic formoterol, according to the arformoterol label.

In two double-blind, randomized, 12-week and multicenter U.S. studies of 1,456 COPD patients, whose mean age was 63 years, and who had a mean forced expiratory volume in 1 second (FEV₁) of 1.3 L (42% of predicted), those on arformoterol

15 mcg twice a day had greater postdose bronchodilation than the placebo group, according to the drug’s label. Bronchodilation was measured as a percent change in FEV₁ from baseline to 12 weeks. Higher doses were studied, but did not provide enough additional benefit to justify their use.

The most common side effects associated with arformoterol treatment included chest pain (7%), back pain (6%), diarrhea (6%), sinusitis (5%), leg cramps (4%), dyspnea (4%), and rash (4%), at rates that were 1%-4% greater than placebo, according to the label.

The label carries a black box warning that long-acting β -adrenergic agonists may increase the risk of asthma-related death, based on a large placebo-controlled study demonstrating an increase in asthma-related deaths in patients treated with the long-acting β_2 -agonist salmeterol, a finding that “may apply to arformoterol,” according to the drug’s label.

—Elizabeth Mechatie

Lung Function Reduced in Diabetes, Large Studies Show

BY JEFF EVANS
Elsevier Global Medical News

WASHINGTON — Diabetic patients have lower lung function than would otherwise be predicted, but the actual trajectory of their lung function parallels that of normal, healthy individuals as they age, Dr. Naresh M. Punjabi, FCCP, said at the annual scientific sessions of the American Diabetes Association.

Studies have shown that types 1 and 2 diabetic patients have reduced forced expiratory volumes, total lung volumes, and diffusion capacities. But because most of these studies have been cross-sectional, it has been hard to “tease out” whether diabetes or reduced lung function came first, said Dr. Punjabi of the division of pulmonary and critical care medicine at Johns Hopkins University, Baltimore.

In one cross-sectional study of 3,254 individuals in the Framingham offspring cohort, both forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) declined significantly, whereas the fasting blood glucose levels of nondiabetic individuals rose. FEV₁ and FVC also were lower than predicted in diabetic participants. The pattern was even stronger in diabetic and nondiabetic former or current

smokers than in those who never smoked. The ratio of FEV₁ to FVC, which is a measure of expiratory airflow obstruction, was not related to fasting blood glucose levels in former smokers and in those who had never smoked (*Am. J. Respir. Crit. Care Med.* 2003;167:911-6).

Another cross-sectional study of 3,911 women aged 60-79 years reported that FEV₁ and FVC were significantly and negatively correlated with insulin resistance and the prevalence of type 2 diabetes after adjustments were made for confounding variables (*Diabetologia* 2004;47:195-203).

“These are two large studies that show a cross-sectional relationship between spirometric measures and metabolic measures,” he said. “The question then becomes, can we prove causality?”

In a longitudinal study of 17,506 patients, 266 patients already had diabetes at the beginning of the study and another 451 developed diabetes during the study’s 15-year follow-up. In spirometric testing performed at baseline and during at least one round of additional testing, both FEV₁ and FVC were 8% lower than their predicted values in patients with diabetes, compared with those who did not have diabetes (*Eur. Respir. J.* 2002;20:1406-12).

“This is a pretty substantial difference

between those who have diabetes and those who don’t,” Dr. Punjabi said. But the longitudinal decline in lung function of diabetic patients was similar to that of nondiabetic patients for both men and women.

It is possible to speculate how diabetes could lead to impaired lung function, Dr. Punjabi said. There are data from post-mortem studies of diabetic individuals to suggest that the lung is a target organ for diabetic microangiopathy, as well as indirect data showing that diabetes may contribute to lower diffusion capacity.

There are fewer data to suggest that impaired lung function predicts future diabetes, but some evidence is beginning to show that such an association might exist, even though plausible biologic mechanisms to support it are “shaky,” Dr. Punjabi said.

Spirometric data on 4,830 men and women in the National Health and Nutrition Examination Survey showed that obstructive lung disease (represented by the FEV₁/FVC ratio) was not significantly associated with the development of diabetes, but restrictive lung disease (signifying a lower FVC) was. The men and women were followed from their first interview and examination in 1971-1975 through 1992-1993. Only 68 patients had

restrictive lung disease, but those who had the disease were 45% more likely to develop diabetes than were those who did not have the lung condition. The associations did not differ according to smoking status (*Diabetes Care* 2004;27:2966-70).

Another study that addressed the effect of baseline pulmonary function on incident diabetes prospectively showed that over the course of a 9-year follow-up in 11,479 patients, both the absolute values of FEV₁ and FVC and the percentage of predicted FEV₁ and FVC were associated with incident diabetes. No relationship was found with the FEV₁/FVC ratio (*Diabetes Care* 2005;28:1472-9).

Investigators in both studies adjusted the analyses for numerous confounding variables.

“The decrease in lung function that we’re talking about here is insufficient to cause any degree of hypoxemia,” thus eliminating it as a possible mechanism to explain how impaired lung function could lead to diabetes, he said.

But low lung function and diabetes risk may be determined by another underlying cause. It is possible that reduced lung function is “not a precursor of diabetes but just a marker of what’s going to happen eventually anyway,” Dr. Punjabi speculated. ■

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 BY DR. MARK J.
 ROSEN, FCCP

PRESIDENT'S REPORT

Embracing a Team Approach

As this is my first month as ACCP President, I would like to offer remarks from my Presidential Address at CHEST 2006 in Salt Lake City. These remarks reflect areas of concern that I hope to address, with the help of ACCP members and partners, during my year as President.

“Three years ago, Dr. Richard Irwin’s presidential address focused the College’s field of vision on the simple but profound concept of patient-focused care. Like all of us, he wants only the best care for his family, and he challenged us to treat every patient as a member of our family.”

“When it comes to our own or families’ health care, we would want a team to help us—specialists to offer opinions or perform procedures, outstanding nurses, respiratory therapists and pharmacists, and the best technology and systems to give us the most accurate diagnosis and most effective treatment.”

“We now need to embrace a team approach in everything we do in our profession, from our daily patient care

to our efforts to engage and improve the system. We do this explicitly in the ICU and in the operating room. I ask that you think of your general inpatient units and your private offices and clinics in the context of a similar team approach. Conducting our professional lives in an atmosphere of collaboration among every person who deals directly or indirectly with every patient will only make patients’ experiences better. In a patient-focused health system, every patient will be treated by a team.”

“Teamwork is reflected in the daily operations of the ACCP. We actively seek out other organizations with similar goals to help us, and accept similar invitations from them. The ACCP, the American Thoracic Society, the Society of Critical Care Medicine and the American Association of Critical-Care Nurses are collaborating on a national level to address a critical care workforce shortage, by working with members of Congress to draft specific legislation to address this crisis. Working as a team, and speaking with a single voice, is surely more powerful than each organization on its own.”

“As individuals and as a College, we need to act in collaboration and coordination with others to be effective. So join a team, and get busy. Form or join a team

at home to improve the care of our patients, and intensify your involvement with the ACCP—we welcome you, and we want your help. For clinicians, join an ACCP NetWork or committee, and get active. Learn more about The CHEST Foundation, and participate.”

“Let me address the new ACCP Fellows directly. You made three pledges, and I ask you to live by them and to make them happen wherever you work. You need to stay current with the literature, and you need to practice according to the best and most current evidence. The ACCP is here to help, as it is the best resource for education in pulmonary, critical care, and sleep medicine in the world. Never stop being a teacher, because the best way to learn something new is to have to explain it correctly to someone else. You also need to love what you do, and you need to have fun. You need to laugh, and you should laugh a lot. In facing your personal and professional challenges and frustrations, if you can laugh about it, you can live with it.”

“Thank you for the honor and the privilege to serve as President of the American College of Chest Physicians. I will work to the best of my ability on behalf of the College, its members, and most of all, our patients.” ■

In-Training Exam, Pulmonary and Critical Care Medicine

Update—October 2006

In early 2005, the training program directors for pulmonary and critical care medicine met to discuss issues relevant to the training of pulmonary and critical care medicine fellows. At the completion of that meeting, one of the recommendations was to investigate the development of an in-training (in-service) examination for fellows. It is the belief that the examination would enable the fellow to determine his/her competence in the areas of medical knowledge and patient care and

enable the program director to effect improvements in the training process.

A working group (question writers) was selected from each of the three organizations participating in the exam development. The Association of Pulmonary and Critical Care Medicine Program Directors, the American College of Chest Physicians, and the American Thoracic Society each provided three members for the group, and a testing agency was contracted to assist with the exam development.

The members of the working group

and the organizations they represent are:

▶ **APCCMPD:** Dr. Doreen J. Adrizzo-Harris, FCCP, *Chair*; Dr. James A. Rowley, FCCP; Dr. Andrew R. Berman, FCCP

▶ **ACCP:** Dr. Brian W. Carlin, FCCP, *Vice-Chair*; LTC Lisa K. Moores, MC, USA, FCCP; Dr. Robert Balk, FCCP

▶ **ATS:** Dr. Susan Murin, FCCP; Dr. Mark R. Tonelli, FCCP; Dr. John G. Mastronarde, FCCP

The actual development of the examination began in late spring 2006. The first step, which has been completed, is the de-

velopment of a detailed content outline for the examination. The working group has selected the various topics that it judged necessary to reflect the knowledge, skills, and attributes that a fellow should possess to practice pulmonary and critical care medicine. This detailed content outline is being used to develop the actual test questions. The next step is writing the test questions. This will be followed by a review of each question for content and accuracy and placing each question into the examination to be given.

The goal is to develop a 100-question examination that will be offered in late April 2007. The examination will be a computer-based examination with the testing “window” being open during the last 2 weeks of April. Details regarding the testing process are now being developed, and registration information and test logistics will be forwarded to all program directors and trainees in early 2007. Following closure of the testing “window,” the working group will review the test results and distribute, to each program director and fellow, the individual, program, and the overall results.

The goal is to develop an examination that will allow the fellow and training program director an effective method to assess a fellow’s performance throughout the program and to utilize assessment results to improve the performance of the fellow and the program.

Details and updates will be posted on the program directors Web site (www.apccmpd.org). ■

Imagine



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THE power of 10

Pulmonary Perspectives

Bronchoscopy and the Solitary Pulmonary Nodule: A New Look

A solitary pulmonary nodule (SPN) may be defined as a round or lobulated lesion < 3 cm in diameter that is completely surrounded by lung. The incidence of SPNs in United States is approximately 150,000 per year. This rate is expected to increase as more screening CT is performed. Since 35% of newly found SPNs are malignant, the diagnosis is essential, because surgical resection of early stage lung cancer improves survival.

Diagnostic tools range from close observation to thoracotomy. Of the available procedures, flexible bronchoscopy (FB) remains the safest for obtaining a tissue diagnosis. Lesion size has long been a key factor influencing the diagnostic yield. Most studies have found the yield of FB drops significantly for lesions < 2 cm in diameter. As a result, current guidelines recommend other procedures for smaller lesions. In recent years, however, investigators have looked at different innovative tools and imaging techniques that may improve bronchoscopic diagnosis of the SPN. This Perspective will review the current status of FB in light of new techniques and question whether current guidelines should be modified based on these advances.

Transbronchial Needle Aspiration

Since the 1980s, many studies have confirmed that the yield of FB for SPNs improves with the addition of transbronchial needle aspiration (TBNA), although lesion size remains a limiting factor. For example, one study of different bronchoscopic sampling modalities to evaluate SPNs or masses reported an overall diagnostic yield of 73%, while the yield for lesions < 2 cm was 54% and 57% for lesions < 3 cm (Chechani. *Chest* 1996; 109:620). The yield of TBNA alone was 51% overall. The diagnosis was made exclusively through TBNA in 8% of cases.

Endobronchial Ultrasound

Endobronchial ultrasound (EBUS) has been used with FB to improve the yield of FB for small peripheral lesions. Using a guide-sheath (EBUS-GS) and a curette to maneuver the guide-sheath if the lesion was difficult to reach, the reported diagnostic yield was 53.3% for lesions < 2 cm and 66.7% for those 2 to 3 cm (Kikuchi et al. *Eur Respir J* 2004; 24:533). The overall yield was 58.3%. Another study used EBUS-GS with the curette technique to localize peripheral lesions followed by transbronchial biopsy (TBBx) and brushings with

fluoroscopic guidance (Kurimoto et al. *Chest* 2004; 126:959). The diagnostic yield was 77%. The yield from TBBx was higher than from brushings: 74% for lesions < 3 cm vs 92% for masses = 3 cm. In another comparison of EBUS-TBBx to TBBx in individuals with peripheral mass lesions, the diagnostic yield of EBUS-TBBx was 75.8% compared with 52.1% for TBBx (Paone et al. *Chest* 2005; 128:3551). As the lesion size decreased, the yield of TBBx declined, while the yield of EBUS-TBBx did not change. For lesions < 2 cm, the sensitivity of EBUS-TBBx was 71% compared with 23% for TBBx. In a study of SPNs not visible by fluoroscopy, EBUS-GS was used to visualize the lesions and guide TBBx (Herth et al. *Chest* 2006; 129:147). The lesion size ranged from 1.4 to 3.3 cm (mean 2.2 cm). The lesions were localized in 89%, and the diagnosis was established in 70% of patients. Combining EBUS-GS with virtual bronchoscopy (VB) for SPNs < 3 cm, the diagnostic yield was 63.3% (Asahina et al. *Chest* 2005; 128:1761). Sensitivity was higher for lesions 2 to 3 cm in diameter (91.7%) compared with lesions < 2 cm (44.4%).

The Ultrathin Bronchoscope

The ultrathin bronchoscope has been used to improve access to peripheral lesions and obtain cytologic specimens with a small brush. A study of peripheral lesions with a mean size of 3.2 cm achieved direct visualization of the lesion in 23.5% of patients (Rooney et al. *Respiration* 2002; 69:63). The yield was 70% for lesions < 3 cm, with an overall yield of 64.7%. The small brush was exclusively positive in 11.8% of cases.

CT in Bronchoscopy

CT is gaining popularity in the field of bronchoscopy. Its roles vary from a pre-procedure imaging technique helping the bronchoscopist plan procedures to continuous imaging during bronchoscopy, known as CT fluoroscopy. One group has evaluated helical CT with multiplanar reconstruction and ultrafast Papanicolaou staining in the bronchoscopic diagnosis of SPNs (Bandoh et al. *Chest* 2003; 124:1985). CT was used to localize the nodule and determine the bronchus leading to it, followed by curette biopsy. The curetting was repeated until positive to a maximum of four attempts. If a positive cytologic result was not obtained, traditional TBBx was performed. A diagnosis was obtained by curetting in 84% of cases. The yield for lesions < 2 cm was 82%, and there was no statistically significant difference in the yields for larger lesions. The accuracy of FB using this technique (91%) was higher than with conventional approaches in a historical control (58%). One study examined CT-guided TBBx in nine patients (Wagner et al. *Respiration* 1996; 63:181). Although feasible, the technique was more difficult than the traditional TBBx.

CT fluoroscopy has been used to guide TBNA for nodes, as well as for nodules or

Impact of Complementary Tools on the Diagnostic Yield of FB Based on Lesion Size

Tool	Author, year	Lesion ≤2 cm, %	Lesion >2 cm, %
STAF*	Sasada et al. 2006	73.2	83.3
Curette	Mori et al. 1989	83.5	N/A
CT-guided TBNA	White et al. 2000	66.7	66.7
EBUS-TBBx	Kurimoto et al. 2004	72.8	82.6
EBUS-TBBx	Kikuchi et al. 2004	53.3 (<2 cm)	66.7 (2-3 cm)
EBUS-TBBx	Paone et al. 2005	71	82.8 (>3 cm)
EBUS-TBBx/VB	Asahina et al. 2005	44.4 (<2 cm)	91.7 (2-3 cm)
ENB	Schwarz et al. 2006	50	72.7

*STAF- Sasada transbronchial angled forceps.

focal infiltrates (White et al. *Chest* 2000; 118:1630). The mean diameter of the lesions was 2.2 cm. The overall accuracy was 83%. A specific diagnosis was obtained in 58% of lesions. A study combining use of the ultrathin bronchoscope with CT guidance for the diagnosis of peripheral lesions (mean diameter 1.4 x 1.1 cm) reported a diagnostic rate of 78.3% (Asano et al. *Nihon Kokyuki Gakkai Zasshi* 2002; 40:11).

Electromagnetic Navigation Bronchoscopy

The first human study using real-time electromagnetic navigation bronchoscopy (ENB) for the diagnosis of peripheral lung masses (including SPNs) was recently reported (Schwarz et al. *Chest* 2006; 129:988). The lesion diameter ranged from 1.5 to 5 cm (mean 3.35 cm). The diagnostic sensitivity of the procedure was 69%. In a prospective study evaluating ENB for peripheral lung lesions and mediastinal lymph nodes, the mean size of the SPNs was 2.28 cm (Gildea et al. *Am J Respir Crit Care Med* 2006 Jul 27, Epub ahead of print). The diagnostic yield was 76% for SPNs, and the yield was independent of size or location.

Many other sampling techniques have been used during bronchoscopy to improve its diagnostic yield for SPNs (Table). Many have been described in small studies and

include the double-hinged curette (Mori et al. *Chest* 1989; 95:304), the newly invented forceps with an angled tip (STAF) (Sasada et al. *Chest* 2006; 129:725), the needle-brush, and others. These techniques need to be validated in larger studies.

There is a prevailing consensus that bronchoscopy has no role for nodules < 2 cm in size. The data suggest, however, that FB can play a valuable role in the diagnosis of SPNs < 2 cm in diameter when one or more of the complementary techniques described here are utilized. The proposed lung cancer guidelines should be revised to include FB in the evaluation of lesions < 2 cm, especially when the risks involved with alternative procedures are considered higher than those with FB. ■

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and

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Editorial Comment

The underlying problem with SPNs is that they may be benign or malignant and one would like to limit diagnostic invasiveness for benign lesions.

Thoracotomy provides the most accurate diagnosis, but at a cost of considerable invasiveness. Most less invasive techniques have lower yields, particularly for smaller lesions. Interestingly, three techniques described in this *Perspective*, electromagnetic navigation bronchoscopy, ultrasound biopsy, and the helical CT reconstruction with curetting and on site cytology, show promise in achieving good yields independent of lesion size. The interpretation of many studies to date has been confounded by

varying definitions of SPNs with respect to lesion size, mixing of SPNs and mass lesions, and varying populations with respect to risk of cancer. Future studies will need to address these issues.

For now, the choice of observation or a particular diagnostic procedure remains a balance of physician suspicion, risk factors, lesion size, local expertise, and patient preference. As more studies emerge, these new techniques may alter that balance. In addition, we should not forget the value of a careful bronchoscopic airway examination in the detection of second, unsuspected lesions.

—Editor

Dr. Deborah Shure,
Master FCCP

Editor,
Pulmonary Perspectives

Dr. Aymar Robles, FCCP

Deputy Editor,
Pulmonary Perspectives

SLEEP STRATEGIES

Improving the Assessment for Obstructive Sleep Apnea in Commercial Driver's License Holders

Obstructive sleep apnea (OSA) is associated with an increased number of at-fault motor vehicle accidents.¹ It has also been shown that commercial driver's license holders (CDL) have an increased prevalence of OSA. This includes a study done earlier this decade in Pennsylvania that indicated over 15% of drivers had an apnea-hypopnea index (AHI) of >5 events per hour.²

Additionally, CDL holders operate vehicles that are typically large, carry toxic or dangerous chemicals, or carry a large number of passengers, which means they need to be held to an even higher standard than that of a regular driver's license holder. However, despite this, these drivers often have economic incentives to drive long distances or in unsafe conditions.

The guideline for assessment of OSA in CDL holders has not been updated in almost a decade. The urgent need to re-evaluate this area came to light in early 2005, and the National Sleep Foundation (NSF), the American College of Chest Physicians Sleep Institute (ACCP-SI), and the American College of Occupational and Environmental Medicine (ACOEM) decided to tackle this important issue.

The tri-society task force was developed, led by Dr. Natalie Hartenbaum, MPH, FACOEM, from the ACOEM; Dr. Barbara Phillips, MPH, FCCP, from the NSF; and Dr. Nancy Collop, FCCP, and Dr. Ilene Rosen, MSCE, FCCP, from the ACCP-SI. An initial meeting with those representatives, plus others from the ACOEM and NSF, was held at NSF headquarters in the summer of 2005. A working plan was developed, and background material was gathered.

The next step was to review the literature in this area, which included not only current regulations, guidelines, and standards already in place but also the guidelines for other countries and pertinent medical literature, including assessment, diagnosis, treatment, and follow-up for OSA.

Following the literature review, a consensus-type conference was held in the spring of 2006 under the guidance of Dr. Mark Rosekind. Attendees to this conference included sleep medicine professionals, occupational medicine professionals, and representatives from all three organizations.

A blueprint was developed for the recommendations, and following the meeting, writing assignments were given to several participants, in addition to other experts in the fields of occupational and sleep medicine. The process was coordinated by Dr.

Hartenbaum, and a draft product was sent out for review in the summer of 2006. The final product was sent to the *Journal of Occupational and Environmental Medicine*, which published the entire article in their September 2006 issue, along with an executive summary, which was also published in *CHEST* in the September 2006 issue, with an accompanying editorial.^{3,4}

It is important to point out that these recommendations have not been adopted at this time by any government agency and are only those of the task force. Because several of the areas covered had relatively weak evidence to guide us, expert opinion was used. This guideline sought to make recommendations on screening, diagnosis, treatment, follow-up, and return to work. It is possible that these recommendations could be extended to other safety-sensitive positions, as well.

The current Federal Motor Carrier Safety Administration (FMCSA) does include a question on its medical examination report for Commercial Driver Fitness Determination, which queries whether the driver has "sleep disorders, pauses in breathing while asleep, daytime sleepiness, or loud snoring." If the

THESE DOCUMENTS WILL GIVE MEDICAL EXAMINERS AND HEALTH-CARE PRACTITIONERS BETTER GUIDANCE ON HOW TO DEAL WITH OSA.

medical examiner obtains a positive answer to this or "detects a respiratory dysfunction that in any way is likely to interfere with the driver's ability," he is instructed to refer the driver to a specialist for further evaluation. Currently, this is the only guidance available regarding screening for OSA in CDL holders.

The recommendations by the task force are more specific and give the medical examiner guidance on when drivers are medically qualified to drive, when they should be able to remain in service but undergo an evaluation for OSA (in-service evaluation), or when they should be taken out of service while undergoing an evaluation (out-of-service evaluation). In-service evaluation categories include items examining sleep history, body mass index, neck circumference, presence of hypertension, an

elevated Epworth sleepiness scale (ESS) score, or a prior OSA diagnosis with mild-to-moderate elevation in AHI (5 to 30) that has not been treated or had compliance with therapy monitored.

Out-of-service evaluation requirements would include a sleepiness- or fatigue-related accident or greatly elevated ESS score (>16) and prior diagnosis of severe OSA (AHI >30) with-

out adequate follow-up.

There is little written about the diagnostic aspect of OSA in prior federal guidelines. CDL drivers are expected to undergo evaluations biannually, and a report written by the Federal Highway Administration in 1991 suggested that polysomnography should be used to make the diagnosis.⁵ The task force recommendations regarding diagnosis of OSA explicitly state that the diagnosis should be determined by a physician and confirmed by polysomnography; baseline polysomnography is preferred, however; and split-night polysomnography is acceptable if severe OSA is documented.

Regarding treatment, the 1991 report recommended continuous positive airway pressure (CPAP) as treatment but offered no guidance as to what was considered successful treatment. Little information was available about surgery or weight loss as options, and no data were available regarding dental appliances. The task force has addressed all these aspects in their recommendations. CPAP is considered the first line of treatment, and devices should be used that can measure adherence to therapy. Surgery, weight loss, and dental appliances are also addressed. The task force stated that a minimum acceptable average use of CPAP is 4 h every 24 h.

Another issue addressed was how long to wait before returning to work once a diagnosis of OSA is made and treatment initiated. This is extremely important to the driver and his company. Prior guidelines stated that drivers should not return to work for a minimum of a month. The task force guidelines suggest that, ideally, the AHI should be reduced to <10 (<5 is preferable) with the CPAP titration; the driver should be contacted by medical personnel within a week of starting CPAP; and adherence to therapy should be checked 2 to 4 weeks after initiation of CPAP. Unlike the recommendations of the Federal Aviation Administration,⁶ the task

force did not recommend a multiple sleep latency test or maintenance of wakefulness test (which the Federal Aviation Administration uses) to re-evaluate objective sleepiness, because there are no data available to suggest that this correlates with fitness to drive (or fly, for that matter). Further information is also given in the task force documents about long-term follow-up, including an annual evaluation by a sleep specialist.

The task force is very hopeful that these documents will give medical examiners and health-care practitioners caring for these drivers better guidance on how to deal with suspected or known OSA. It is further hoped that if adopted in some manner by the federal agencies, this guidance will help decrease fatigue- and sleepiness-related accidents in this population. Remember, trucks weighing more than 5 tons have a sevenfold risk of fatality to the other motorist than to the truck occupants. The members of the task force hope this is a big step toward making our highways safer for all. For all of you taking care of such patients, these documents are a must-read! ■

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NEWS FROM THE COLLEGE



This Month in *CHEST*: Editor's Picks



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

- ▶ **A 30-Year-Old Man With a History of Polysubstance Abuse and Hepatitis C Presents With Exertional Dyspnea and Patchy Ground-Glass Opacities.** *Dr. Francis Girvin and Dr. Ioannis Vlahos*
- ▶ **Cellular vs Fibrosing Interstitial Pneumonias and Prognosis: A Practical Classification of the Idiopathic Interstitial Pneumonias and Pathologically/Radiologically Similar Conditions.** *Dr. Andrew Churg and Dr. Nestor L Müller*
- ▶ **Changing the Work Environment in ICUs To Achieve Patient-Focused Care: The Time Has Come.** *Dr. Kathleen McCauley and Dr. Richard S. Irwin, FCCP*
- ▶ **An Outbreak of *Burkholderia cepacia* Associated With Contamination of Albuterol and Nasal Spray.** *Dr. Concepcion F. Estivariz, et al*
- ▶ **Development of a Contemporary Bleeding Risk Model for Elderly Warfarin Recipients.** *Dr. Theresa I. Shireman, et al*
- ▶ **Tracheal Replacement by Allogenic Aorta in the Pig.** *Dr. Sophie Jaillard, et al*

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Ambassadors Group Welcomes Cindy Johnson as New Chair

It is with great pleasure that The CHEST Foundation announces that Cindy Johnson, wife of Dr. Robert G. Johnson, FCCP, President of The CHEST Foundation, is the Ambassadors Group Chair for 2006-2007. This is a reprise for Cindy, as she was part of the original planning group that created the Ambassadors in 2001, and she served as its first Chair when her husband was ACCP President in 2000-2001.

Cindy is wonderfully committed to family and community work. Many of her volunteer hours revolve around her children's activities and educational institutions. She is presently President of the Saint Louis University Hospital Auxiliary and Director on the board of St. Michael's School.

As Chair of the Ambassadors Group for 2006-2007, her objectives are to increase membership and promote the excellent

programs and projects already developed. These include the *Stories at the End of Life*, the healthy lungs education programs, the Love Your Lungs™ wristbands, and the new CD, "Make the Choice: Tobacco or Health?"

Cindy values the Ambassadors Group as a link between the ACCP's professional members and their families. As such, the Ambassadors Group complements and expands the role of the ACCP in society. The Ambassadors give spouses, family members, and friends of ACCP members an opportunity

to act upon their shared commitment to tobacco prevention, clinical research, humanitarian service, and critical care. She takes pride in the Ambassadors Group's volunteer efforts on behalf of ACCP members and The CHEST Foundation. She looks eagerly toward the productive year ahead. ■



CINDY JOHNSON

AMERICAN COLLEGE OF CHEST PHYSICIANS

2006-2007

November 19 - 22

11th Congress of the Asian Pacific Society of
Respirology (APSR)
Kyoto, Japan

January 18 - 21

Sleep Medicine 2007
Scottsdale, Arizona

March 16 - 18

Celebration of Pediatric Pulmonology 2007
San Antonio, Texas

June 22 - 24

Noninvasive Mechanical Ventilation 2007
Montréal, Québec, Canada

June 22 - 25

World Asthma Meeting
Istanbul, Turkey

August 24 - 27

Sleep Medicine Board Review Course 2007
Phoenix, Arizona

August 24 - 28

Critical Care Board Review Course 2007
Phoenix, Arizona

August 28

Lung Pathology 2007
Phoenix, Arizona

August 28

Mechanical Ventilation 2007
Phoenix, Arizona

August 28

American Board of Internal Medicine (ABIM)
Critical Care SEP Module
Phoenix, Arizona

August 28

American Board of Internal
Medicine (ABIM) Pulmonary Disease
SEP Module
Phoenix, Arizona

August 29 - September 2

Pulmonary Board Review Course 2007
Phoenix, Arizona

October 20 - 25

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ACCP WORLDWIDE

ACCP Exhibit at ERS a Popular Spot

BY RICH WATERS

Vice President, ACCP Marketing Division

The annual European Respiratory Society (ERS) meeting provides an excellent opportunity for the ACCP to meet and service current and prospective members. Sixteen percent of ACCP members live outside of the United States and Canada, and many attend the ERS meeting and greatly appreciate the ACCP presence. In September, the ACCP exhibit hall booth at ERS, staffed by ACCP associates and leadership, provided a friendly full-service “way station” for members. The booth was busy, at times overflowing, with members who met with other members and colleagues and ACCP leadership. Many renewed their membership and learned about new ACCP products and benefits. A large variety of ACCP products and programs were displayed and promoted. Sales of the ACCP education products were brisk, with the pulmonary,

critical care, and sleep syllabus books and CDs being the most popular items.

The new international ACCP e-membership program was enthusiastically received. Available in all countries outside of the United States and Canada, it offers the same benefits as traditional membership but at a lower cost. All publications, including *CHEST*, are provided electronically. Membership prices are very affordable and vary by country based on the World Bank’s country classification system. Thirty-three new members registered during the meeting, in addition to 25 renewals—a new record high. Special congratulations to Dr. Sanjeev Kumar Mehta, FCCP, Governor, West Region, India, for personally recruiting and sponsoring seven new members during the meeting!

Watch for the ACCP traveling exhibit booth at your educational events. It provides an excellent opportunity to learn more about the ACCP and to meet and share your thoughts and ideas. ■

ERS Perspectives

“Participation in the major chest meetings around the world provides the leadership of the respective societies an opportunity to interact with their counterparts. The world is becoming smaller by the day, and this level of interaction and cooperation allows leaders to learn from each other.”

Dr. W. Michael Alberts, FCCP
 Immediate Past President, ACCP

“This meeting has become one of the major pulmonary disease congresses of the year and reflects the increasing development of pulmonary medicine in the European area.”

Dr. Gerald L. Baum, FCCP
 Attendee

“This was a great opportunity to meet with ACCP members at the booth and to discuss how ACCP can meet their educational needs.”

Al Lever, MA, FCCP(Hon)
 Executive VP and CEO, ACCP

“It’s always great to see the enthusiasm from the international community—it reinforces the fact that ACCP has members in over 100 countries, and that *CHEST* receives 65% of its submissions from authors outside of North America. We received many positive comments about the recent changes in *CHEST*, implemented by Dr. Irwin since he took the reins as Editor in Chief last year.”

Steve Welch
 Vice President and Executive Editor,
 CHEST



Missed a Session at CHEST 2006?

CHEST 2006 sessions will be made available in a variety of formats that include audio reproductions of LIVE lectures. Faculty handouts are included for select presentations (as released by faculty for inclusion).

For more information, or to order your audio recordings now, call (800) 343-2227 (US) or (847) 498-1400 (outside of US). (All sessions will be offered in prepackaged bundles by clinical topic.)



World Asthma Meeting (WAM) 2007

June 22-25, 2007
 Istanbul, Turkey

The theme of WAM 2007 is “Bridging Various Aspects of Asthma.” Professor Elif Dagli, Chair of the WAM Committee, notes, “The WAM Committee wished to discuss regional perspectives of asthma in a city on two different continents, historically and geographically connecting Northern Africa, Middle East, Central Asia, and East Europe. Please come and let yourself

be spoiled with the famous Turkish hospitality.” The scientific program will include postgraduate courses, keynote lectures, plenary sessions, symposia, and hot topic sessions on obesity and asthma; severity vs control; new insights in immunopathogenesis; and safety of LABAs. The ACCP serves on the WAM 2007 Committee, and ACCP members will be participating in the program. More information is available at www.wam2007.org/.

ACCP Workshop Targets Often Undetected Problem in COPD

Anxiety and depression, common comorbidities in patients with COPD, often remain undiagnosed and untreated. To address these issues, the ACCP, as a Clinical Pulmonary Medicine NetWork project, hosted “Detection and Management of Depression and Anxiety in COPD—A Multidisciplinary Scientific Workshop” on September 15 and 16.

The workshop was sponsored by a National Institute of Mental Health grant, with additional support from the Alpha-1 Foundation and COPD Foundation. Attendees and faculty represented several societies and stakeholders involved in this issue.

The workshop featured presentations by a multidisciplinary faculty and focused on the prevalence of these comorbidities in the COPD

population, approaches to screening and diagnosis, and evaluation of the current knowledge for a variety of management models. Speakers, including patients, also addressed barriers to identification and management of anxiety/depression in culturally diverse populations and the impact of anxiety/depression screening and management on public policy.

In addition to the formal presentations, breakout sessions afforded the participants opportunities to discuss and make several recommendations for improved detection and management of anxiety and depression as a means of improving quality of life for COPD patients and for future research in this area. Publication of the proceedings and recommendations from this workshop is planned. ■

NEWS FROM THE COLLEGE



How We Keep Evidence-Based Guidelines Up to Date

BY JULIA HEITZER, MS
Research Specialist
ACCP Health and Science Policy

The American College of Chest Physician's (ACCP) Health and Science Policy (HSP) Committee is charged with ensuring that all evidence-based clinical practice guidelines published by the College are current and up to date. There is a formal review process, which guarantees our members are accessing current and timely clinical recommendations in health, science, and clinical policy in chest medicine.

The HSP Guidelines Subcommittee completes an annual review of all guidelines and determines if a guideline remains current, if there are new studies available that may warrant an update or partial update, or if the guideline needs retirement.

The lead author/editor of the guideline, the HSP Committee liaison to the guideline panel, and relevant NetWorks with knowledge of this clinical topic, are asked for their expert opinion on the status of the guideline relative to the current evidence.

These individuals make a recommendation to the HSP Committee as to whether the guideline should be re-affirmed, revised, or retired, using one of the five rankings:

- ▶ The guideline is current as is and should be reviewed in 1 year.
- ▶ New evidence is available that may be useful; however, a revision is not mandatory at this time, and the guideline should be reviewed in 1 year.
- ▶ There is new evidence available that warrants revision of the following section(s)/chapter(s) of this guideline.
- ▶ There is sufficient new evidence available to warrant a complete revision of this guideline.
- ▶ This guideline is not current and should be retired.
- ▶ If revision is recommended, current and relevant references are provided.

At the ACCP's annual CHEST meeting, the HSP Committee convenes and discusses the status of all guidelines using this information and appropriately classifies each document into one of the

four categories: (1) new evidence has been published, but it does not warrant an update (readers are encouraged to search the current literature as a supplement to using this guideline); (2) new evidence has been published that would warrant an update; (3) the guideline is up to date and no changes are necessary; or (4) the guideline is outdated, and retirement is necessary (guideline is removed from the Web site).

Important consideration is given to supplements (multichapter guidelines) when updating only a single chapter. This can pose a problem because the grading system used initially has currently been updated, and updating only

THE HSP GUIDELINES SUBCOMMITTEE COMPLETES AN ANNUAL REVIEW OF ALL GUIDELINES AND DETERMINES IF A GUIDELINE REMAINS CURRENT.

portions of the guideline could result in inconsistency in terms of the way the recommendations are graded (strength and level of evidence). It also causes complexities when the entire guideline is updated in the future, which is why the HSP Committee steers away from single chapter updates. In certain cases, the HSP Committee allows updates using the former grading system, as in the case of the Diagnosis and Management of Pulmonary Arterial Hypertension guideline, which is currently in process.

The guidelines currently being reviewed this year at CHEST 2006 include the following: Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery, Weaning and Discontinuing Ventilatory Support, Assessment of Diagnostic Tests for Ventilator-Associated Pneumonia, Device Selection and Outcomes of Aerosol Therapy, and Medical and Surgical Treatment of Parapneumonic Effusions.

Please visit the HSP Web site at www.chestnet.org/education/guidelines for more information. ■

Practice Management Update

The updated Medicare/Medicaid Relationship Brochure is now available in downloadable format on the Centers for Medicare & Medicaid Services MLN Publications Page located at www.cms.hhs.gov/MLNProducts/downloads/Relationship_Brochure.pdf on the CMS Web site.

The brochure discusses the relationship between Medicare beneficiaries

who have limited income and possible resources from their state Medicaid program to help pay for their out-of-pocket medical and prescription expenses. For such persons who are eligible for full Medicaid coverage, the Medicaid program supplements Medicare coverage by providing services and supplies that are available under their state's Medicaid program. ■

ACCP Recognizes "Friends of the College"

The ACCP and The CHEST Foundation are proud to recognize the following "Friends of the College" for their financial support of College activities during 2006. We would also like to thank the ACCP Industry Advisory Council for their continued commitment to work with the College on community service projects and other initiatives of mutual importance. (Note: this list reflects support received by the date of publication.)

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In ICU, Risks of Tight Glucose Control May Outweigh Benefits

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

BARCELONA — The benefits of tight glucose control with intensive insulin therapy may not be worth the risk of hypoglycemia for critically ill patients, Dr. Jean Charles Preiser said at the annual congress of the European Society of Intensive Care Medicine.

Although the overall risk of death was not significantly increased among such patients, the European GluControl study did find a significant increase in the risk of death among those who had at least one episode of severe hypoglycemia, said Dr. Preiser of the Centre Hospitalier Universitaire de Liège, Belgium.

The trial needed 3,500 patients to confirm the 4% decrease in mortality reported in a similar 2001 study (N. Engl. J. Med. 2001;345:1359-67). However, GluControl was halted in March 2006 because of a trend toward higher mortality in the experimental group and many unintended protocol violations.

Dr. Preiser presented an analysis of the 1,091 patients enrolled at the time of suspension.

ICU patients were randomized to either tight glucose control (80-100 mg/dL) or conventional control (140-180 mg/dL). Their mean age

was 65 years. The mean Apache II score was 20, and the mean Sepsis-Related Organ Failure Assessment (SOFA) score was 7. The mean ICU stay was 5 days. Diabetes was more prevalent in the conventional group (24% vs. 16%), but most patients were not insulin dependent.

The mean glycemic level achieved in the tight control group was 118 mg/dL—higher than the upper limit allowed in the study protocol. In the conventional group, the mean glycemic level was 144 mg/dL.

In all, 97% of the tight control group received insulin, compared with 67% of the conventional group. Severe hypoglycemia (less than 40 mg/dL) was more common in the tight control group than in the conventional group (10% vs. 3%).

ICU mortality was not significantly different between the groups (12% tight control vs. 9.75% conventional control). But the difference became significant when the groups were subdivided into those who experienced at least one episode of severe hypoglycemia and those who did not (18% vs. 11.6%).

After correcting for other risk factors (age, Apache II scores, and SOFA scores), patients in the tight control group had a nonsignificant increase in their risk of death. ■

ICUs With MRSA Patients Put Subsequent Occupants at Risk

BY MARY ANN MOON
Elsevier Global Medical News

Patients admitted to ICU rooms previously occupied by patients infected with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci are at elevated risk of acquiring those infections, reported Dr. Susan S. Huang of Brigham and Women's Hospital, Boston, and her associates.

The researchers reviewed the records of patients admitted to eight adult ICUs at Brigham during 2003-2005. All the ICUs had a 10-bed capacity, and they included medical, cardiac, and general surgery units.

A total of 7,629 patients (10,151 ICU room admissions) were identified as candidates for acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) during their ICU stays, and 7,806 (10,349 ICU room admissions) were candidates for vancomycin-resistant enterococci (VRE) acquisition. Patients who stayed in a room previously occupied by a MRSA carrier had a 3.9% risk of acquiring MRSA,

higher than the 2.9% risk of patients who stayed in a room previously occupied by a MRSA-negative patient. "This 1% excess risk represented 5.1% of all ICU MRSA acquisition during the study period and translated to a 1.1% population attributable risk among the exposed, or 1 in 94 exposed room stays," Dr. Huang and her associates said (Arch. Intern. Med. 2006;166:1945-51).

Similarly, patients who stayed in a room previously occupied by a VRE carrier had a 4.6% risk of acquiring VRE, higher than the 2.8% risk of patients who stayed in a room previously occupied by a noncarrier. "This 1.8% excess risk represented 6.8% of all ICU VRE acquisition during the study period and translated to a 1.7% population attributable risk among the exposed, or 1 in 59 exposed room stays," they said.

The excess risk occurred despite the hospital's room cleaning procedures at discharge, which exceed CDC and Healthcare Infection Control Practices Advisory Committee 2003 national guidelines. ■



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CPAP Withdrawal Altered Brain Function in Sleep Apnea

BY KATE JOHNSON
Elsevier Global Medical News

MONTREAL — Sleep apnea patients receiving continuous positive airway pressure therapy have changes in brain function that can be seen with functional magnetic resonance imaging when the therapy is withdrawn for just two consecutive nights.

"The brains of these patients must work

harder, and possibly in less efficient ways, to perform at the same level [as when they are on the therapy]," said Mark S. Aloia, Ph.D., who reported the findings at the 8th World Congress on Sleep Apnea.

His study included eight subjects with moderate to severe sleep apnea who were compliant with continuous positive airway pressure (CPAP) therapy.

The subjects were asked to complete a cognitive function test called the N-back

test while undergoing functional magnetic resonance imaging (fMRI) of their brains.

The testing was performed both when patients

were compliant with CPAP (at least 2 consecutive nights) and when the therapy had been withdrawn for 2 consecutive nights.

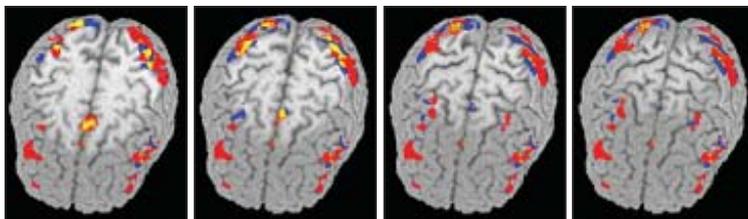
While subjects performed similarly both on and off CPAP therapy (because of extensive task training), the fMRI showed significant differences in which regions of their brains were activated in the presence or absence of CPAP, said Dr. Aloia, who is director of sleep research at National Jewish Medical and Research Center in Denver.

Specifically, there was significantly greater activation of the left middle frontal gyrus and a trend toward greater activation of the right inferior parietal regions when CPAP was withdrawn.

In contrast, when patients had been treated with CPAP, there was significantly more activation of the right middle frontal gyrus.

The findings lend support to the hypothesis that untreated sleep apnea creates an inefficiency in brain function, Dr. Aloia said.

"There seems to be a compensatory response of the brain off CPAP such that subjects are using more brain resources to perform at the same level," he said in an interview. ■



COURTESY DR. MARK S. ALOIA

Red areas in MRI images represent extra activity, possibly compensatory in nature, when CPAP is removed. Blue areas represent recovery with CPAP treatment.

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Nasal Influenza Vaccine Effective in Children

BY GLENDA FAUNTLEROY
Elsevier Global Medical News

Young children with asthma or a history of respiratory tract infections may have an alternative to the standard influenza shot, according to findings of two recent studies.

The only vaccine approved for use in children is the injectable trivalent inactivated influenza vaccine (TIV). Two new studies suggest that the live attenuated influenza vaccine (LAIV, FluMist; MedImmune)—administered nasally—may be a viable option, according to the investigators.

The two studies aimed to compare the safety and efficacy of CAIV-T, an investigational refrigerator-stable form of LAIV, with TIV during one flu season in chil-

bronchitis, and pneumonia, responded to the nasal influenza vaccine (Pediatr. Infect. Dis. J. 2006;25:870-9).

Dr. Shai Ashkenazi and colleagues studied 2,085 children between the ages of 6 and 71 months and divided participants into CAIV-T and TIV groups. Each group was given two doses of either vaccine about 35 days apart. Surveillance time and reporting of adverse reactions or reactogenicity events were reported in similar fashion to the asthma study.

The authors found there were fewer

episodes of influenza in the CAIV-T group (2.3%) than the TIV (4.8%), and concluded that CAIV-T provided “superior protection against the influenza strains,” with an overall efficacy of 53%.

The results of both studies confirm what health care providers have experienced in the past. “These results are not surprising at all,” Dr. W. Paul Glezin, professor of pediatrics at the Baylor College of Medicine in Houston, said in an interview. “We have been testing LAIV for more than 20 years [at Baylor] and have

gotten better influenza protection in young children from LAIV.”

Dr. Glezin added that he has found the immunity of the intranasal vaccine often lasts through a second flu season, unlike that of the influenza injection. Health care providers also are aware of the negative perception the injection has with young patients.

“What young children often react to most is getting a shot,” said Dr. Glezin. “It’s much easier to give them the nasal spray than the intramuscular vaccine.” ■

‘WHAT YOUNG CHILDREN OFTEN REACT TO MOST IS GETTING A SHOT. IT’S MUCH EASIER TO GIVE THEM THE NASAL SPRAY THAN THE INTRAMUSCULAR VACCINE.’

dren with asthma and respiratory infections, respectively.

For children with asthma or other respiratory infections, influenza can exacerbate their conditions. Despite this potential for increased illness, however, according to one study, 75%-90% of children with asthma do not receive the recommended annual influenza vaccine (Pediatr. Infect. Dis. J. 2006;25:860-9).

In the asthma study, 2,229 children and adolescents with asthma aged 6-17 years participated and were divided into two treatment groups—1,114 to be administered one intranasal dose of CAIV-T and 1,115 to receive an intramuscular injection of TIV. The study was conducted during the flu season spanning Oct. 4, 2002, to May 31, 2003.

During the study, all of the participants underwent a screening period before the vaccination and 15 days afterward. During this time, the parents/guardians recorded the children’s daily asthma symptoms.

The parents/guardians also kept a diary until May 31, 2003, to record any adverse reactions requiring medication or health care provider visit or reactogenicity events such as fever, vomiting, and headache.

At the end of the observation period, the authors found no significant difference between the CAIV-T and TIV groups in asthma exacerbation after the vaccinations, and the incidence of confirmed influenza illness was 4.1% in the CAIV-T group, compared with 6.2% in the TIV group.

According to lead author Dr. Douglas M. Fleming and his colleagues in the CAIV-T Asthma Study Group, CAIV-T had a “significantly greater relative efficacy of 35%, compared with TIV, in this high-risk population.”

Researchers in the CAIV-T Study Group, based in Birmingham, England, found similar results in how young children with recurrent respiratory tract infections, including common colds,



The following is a brief summary. Please consult complete prescribing information.

CONTRAINDICATIONS: MAXIPIME® is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics. **WARNINGS:** BEFORE THERAPY WITH MAXIPIME (CEFEPIME HYDROCHLORIDE) FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO MAXIPIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

In patients with impaired renal function (creatinine clearance ≤ 60 mL/min), the dose of MAXIPIME should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms. (See specific recommendations for dosing adjustment in **DOSAGE AND ADMINISTRATION** section of the complete prescribing information.) During postmarketing surveillance, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (see **ADVERSE REACTIONS: Postmarketing Experience**). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules. However, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after hemodialysis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including MAXIPIME, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.” After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS: General: Prescribing MAXIPIME in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. As with other antimicrobials, prolonged use of MAXIPIME may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient’s condition is essential. Should superinfection occur during therapy, appropriate measures should be taken. Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated. Positive direct Coombs’ tests have been reported during treatment with MAXIPIME. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs’ testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs’ test may be due to the drug. MAXIPIME should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of MAXIPIME. The effect of lower doses is not presently known.

Information for Patients: Patients should be counseled that antibacterial drugs including MAXIPIME should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When MAXIPIME is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by MAXIPIME or other antibacterial drugs in the future.

Drug Interactions: Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with MAXIPIME because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. **Drug/Laboratory Test Interactions:** The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinistix® tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term animal carcinogenicity studies have been conducted with cefepime. A battery of *in vivo* and *in vitro* genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast clastogenesis assay, and cytogenetic and micronucleus assays in mice were conducted. The overall conclusion of these tests indicated no definitive evidence of genotoxic potential. No untoward effects on fertility or reproduction have been observed in rats, mice, and rabbits when cefepime is administered subcutaneously at 1 to 4 times the recommended maximum human dose calculated on a mg/m² basis. **Use in Pregnancy—Teratogenic effects—Pregnancy Category B:** Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the recommended maximum human dose calculated on a mg/m² basis) or to mice at doses up to 1200 mg/kg (2 times the recommended maximum human dose calculated on a mg/m² basis) or to rabbits at a dose level of 100 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m² basis). There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Cefepime is excreted in human breast milk in very low concentrations (0.5 µg/mL). Caution should be exercised when cefepime is administered to a nursing woman. **Labor and Delivery:** Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated. **Pediatric Use:** The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of

MAXIPIME (cefepime hydrochloride) in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and safety data from pediatric trials (see **CLINICAL PHARMACOLOGY** section of the complete prescribing information.) Safety and effectiveness in pediatric patients below the age of 2 months have not been established. There are insufficient clinical data to support the use of MAXIPIME in pediatric patients under 2 months of age or for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* type b. IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL EFFICACY IN THIS SETTING SHOULD BE USED. **Geriatric Use:** Of the more than 6400 adults treated with MAXIPIME in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients. Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures. (See **WARNINGS** and **ADVERSE REACTIONS** sections of the complete prescribing information.) This drug 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 renal function should be monitored. (See **CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and DOSAGE AND ADMINISTRATION** sections of the complete prescribing information.)

ADVERSE REACTIONS: Clinical Trials: In clinical trials using multiple doses of cefepime, 4137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g IV q12h). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse events was very similar at daily doses of 500 mg, 1 g, and 2 g q12h (0.8%, 1.1%, and 2.0%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommended doses. The following adverse events were thought to be probably related to cefepime during evaluation of the drug in clinical trials conducted in North America (n=3125 cefepime-treated patients).

TABLE 1
Adverse Clinical Reactions Cefepime Multiple-Dose Dosing Regimens Clinical Trials—North America

INCIDENCE EQUAL TO OR GREATER THAN 1%	Local reactions (3.0%), including phlebitis (1.3%), pain and/or inflammation (0.6%)*; rash (1.1%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting

*local reactions, irrespective of relationship to cefepime in those patients who received intravenous infusion (n = 3048).

At the higher dose of 2 g q8h, the incidence of probably-related adverse events was higher among the 795 patients who received this dose of cefepime. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%). The following adverse laboratory changes, irrespective of relationship to therapy with cefepime, were seen during clinical trials conducted in North America.

TABLE 2
Adverse Laboratory Changes Cefepime Multiple-Dose Dosing Regimens Clinical Trials—North America

INCIDENCE EQUAL TO OR GREATER THAN 1%	Positive Coombs’ test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, WBC

*Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorus were not reported.

A similar safety profile was seen in clinical trials of pediatric patients (See **PRECAUTIONS: Pediatric Use**).

Postmarketing Experience: In addition to the events reported during North American clinical trials with cefepime, the following adverse experiences have been reported during worldwide postmarketing experience. Because of the uncontrolled nature of spontaneous reports, a causal relationship to MAXIPIME treatment has not been determined.

As with some other drugs in this class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures have been reported. Although most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. (See also **WARNINGS**.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. Precautions should be taken to adjust daily dosage in patients with renal insufficiency or other conditions that may compromise renal function to reduce antibiotic concentrations that can lead or contribute to these and other serious adverse events, including renal failure.

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported. **Cephalosporin-class adverse reactions:** In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

OVERDOSAGE: Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability. (See **PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the complete prescribing information.)

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