

CHEST *Physician*

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Whether antiangiogenesis agents can be used alone or should be used with other drugs must be worked out, said Dr. Roy Herbst.

Agents Hold Hope in Advanced Lung Cancer

BY JANE SALODOF
MACNEIL

Elsevier Global Medical News

ATLANTA — A year after bevacizumab proved that angiogenesis inhibition can help patients with non-small cell lung cancer live longer, a second generation of antiangiogenesis agents is showing activity against advanced, metastatic lung disease.

Phase II trials of sunitinib (Sutent), sorafenib (Nexavar), and an experimental drug called ZD6474 (Zactima) all reported progression-free survival rates of 11% or more at the annual meeting of the American Society of Clinical Oncology.

Because each drug hits more cellular targets than does

bevacizumab (Avastin), investigators voiced hope that the new agents will be more effective. Two of the drugs—sunitinib and sorafenib—have already been approved for renal cell carcinoma. Sunitinib also has an indication for gastrointestinal stromal tumors that are refractory to imatinib (Gleevec).

Along with the possibility of better therapies, however, the three trials renewed concerns about the toxicity of antiangiogenic agents. Investigators reported cavitation and hemorrhage leading to treatment-related deaths. Rash, hand-foot syndrome, and controllable hypertension also were seen.

“More than ever, we need

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Gene Tool Predicted Recurrence After Early-Stage NSCLC

‘Metagene’ test revealed high-risk cases.

BY HEIDI SPLETE
Elsevier Global Medical News

A test using genetic microarray technology was significantly more accurate than were clinical factors at predicting lung cancer recurrence, according to data from a small but promising study.

“Lung cancer leads to more deaths than breast, prostate, or ovarian cancer in the United States, so if one could find an opportunity to improve patient care in any little way, it would make a huge difference,” Dr. Anil Potti, the study’s lead researcher, said in an interview.

Dr. Potti of Duke University in Durham, N.C., and his colleagues studied three groups of patients with stage IA non-small cell lung cancer (NSCLC). They used multiple gene expression profiles, termed “metagenes,” to stratify patients’ recurrence risk (*N. Engl. J. Med.* 2006;355:570-80).

Although the researchers reviewed patients with stage I, II,

and IIIA lung cancer, the current published study focused on stage IA patients. These patients do not normally receive chemotherapy after surgery, despite previous research that shows a 25% cancer recurrence rate within 5 years.

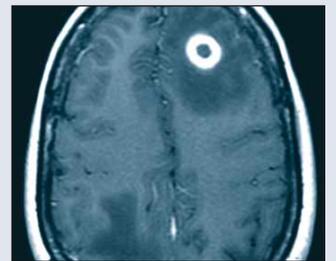
“We could see clearly that about a third of stage IA patients are very high risk based on genetic profiling—high risk meaning that their chance of recurrence within 2 years was about 80%,” said Dr. Potti, of Duke’s Institute for Genome Sciences and Policy.

Clinical staging is a crude measure of a patient’s fitness for chemotherapy, Dr. Potti said. His question: Are there other molecular or biologic phenotypes that would define patients better than clinical stage?

Tumor samples removed from patients during surgery were used for gene expression measurement with microarray technology. The researchers

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Review Backs Low-Dose Steroids

BY BRUCE JANCIN
Elsevier Global Medical News

LISBON — After decades of controversy, a consensus has emerged that corticosteroids provide major benefits in patients with severe sepsis or septic shock, Dr. Djillali Annane said at the 12th International Congress on Infectious Diseases.

The benefits, as shown in multiple randomized placebo-controlled trials, are improved 28-day mortality, shorter shock duration, improved hemodynamics, reduced organ dysfunction, and less systemic inflammation.

It should be emphasized that these benefits accrue only with low-dose corticosteroids administered for at least 5 days, and only in the sizable patient subsets having adrenal insufficiency or refractory septic

shock, said Dr. Annane of the Versailles Saint-Quentin-en-Yvelines University Garches, France.

Much of the lengthy controversy in this field was the result of great heterogeneity in clinical trials, particularly those done before 1992. For example, steroids for septic shock fell into disfavor all through the 1980s and 1990s because multiple trials before 1992 showed no benefit. That’s because these

negative studies used short-course, high-dose corticosteroids, Dr. Annane explained. Today, with the benefit of hindsight, it can be emphatically stated that no evidence supports the use of such therapy, he said at the congress, which was sponsored by the International Society for Infectious Diseases.

Dr. Annane was first author of

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Lung Metagene Model Tested

Gene Tool • from page 1

developed a risk profile for each patient based on the expression patterns of many genes.

The metagenes with the strongest predictive values included several that have demonstrated clinical relevance in NSCLC. For example, metagene 19 represented angiogenesis, which is a proven target for therapy in cancer patients.

In a training cohort of 89 patients enrolled through the Duke Lung Cancer Prognostic, the lung metagene model was 93% accurate in predicting cancer recurrence. In contrast, a predictive model using only clinical data was 64% accurate.

The researchers validated the genomic test by comparing the microarray data with data from two multicenter studies of lung cancer patients. The comparison involved 25 clinical samples from the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial and 84 samples from the Cancer and Leukemia Group B (CALGB) 9761 trial; the trials represented a full range of clinical outcomes.

Overall, the accuracy of genomic tests was 72% in the ACOSOG group and 79% in the CALGB group at

predicting the patients' outcomes.

In addition, a Kaplan-Meier analysis showed that the lung metagene model was significantly better at predicting recurrence than any of several clinical factors: disease stage, tumor diameter, nodal status, age, sex, histologic subtype, and smoking history.

The promising results have inspired a prospective, multicenter clinical trial to begin early in 2007 that will include 50-60 centers in the United States and Canada. The trial will be cosponsored by the Cancer and Leukemia Group B and the National Cancer Institute, and will include about 1,200 stage IA lung cancer patients.

Although genomic profiling needs to be validated prospectively, the tool is readily available and affordable. It costs about \$1,000 to run one test on a single patient, and one test generates the data needed to assess the patient's cancer recurrence risk.

Unpublished findings from Dr. Potti's study group suggest that the genomic data can be used to predict which type of chemotherapy a patient will respond to. "The advantages of genomic profiling are many—it is not just prognosis," he said. "There is definitely an element of trying to predict response to therapy." ■

Dr. Gerard A. Silvestri, FCCP, comments: *This article has important implications for how we stratify risk in patients with lung cancer. Clinicians have been frustrated for years at the recurrence rates and subsequent deaths of those with early stage lung cancer who undergo surgery. To date, there have been no tests that reliably predict recurrence. This study suggests that with genetic microarray technology, one can more accurately predict who will recur. This is an important breakthrough, because currently we do not offer adjuvant chemotherapy for patients with resected stage I disease, as it has not been shown to work in this group.*

Old Age Is No Barrier to 'Switch Therapy' for CAP

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

SAN DIEGO — Advanced age by itself should not be a barrier to switching a patient with community-acquired pneumonia from intravenous to oral antimicrobial therapy soon after the patient shows clinical improvement, Dr. Paolo Rossi said in a poster presentation at the International Conference of the American Thoracic Society.

An observational study of 2,648 adult patients at 40 hospitals in 13 countries showed that, regardless of age, about two-thirds were discharged within 24 hours of meeting the criteria for "switch therapy." Of 372 patients aged 85 years or older, 65% were discharged in this early time frame, as were 68% of 1,161 patients aged 65-84 years and 72% of 1,115 patients aged 18-64 years.

No deaths occurred in the youngest group after switch therapy, and mortality was low among the older groups: 9 deaths (1.6%) of the 554 switch-therapy patients in the 65-84 age group and 2 deaths (1.2%) of the 164 patients in the oldest cohort.

The study shows that frail elderly patients with community-acquired pneumonia (CAP) can handle switch therapy, said Dr. Rossi of S. Maria della Misericordia Hospital in Udine, Italy. "Even if they are over 90 they can, more or less," he said in an interview.

He and his coinvestigators reviewed records of CAP patients who were entered into the Community-Acquired Pneumonia Organization database from June 2001 to May 2005. The database includes hospitals in the United States, and the study coordinator was based at the University of Louisville (Ky.).

The study relied on American Thoracic Society guidelines for time to switch therapy. Patients had to meet four criteria to be considered candidates for a switch:

improvement in cough and shortness of breath; at least 8 hours without a fever; leukocytosis reduced by at least 10% from the previous day; and tolerance of "oral intake with adequate gastrointestinal absorption."

The investigators considered patients to be candidates for hospital discharge once they met the above criteria for oral therapy, a diagnostic work-up was completed, any comorbidity was treated, and social needs were met. Any discharge within 24 hours of the patient's meeting the criteria for switch therapy was considered an early discharge.

Of the oldest patients, 90% were classified as being at high risk—a much larger proportion than in any other age group. Nonetheless, 51.6% met the criteria for switch therapy on or before the 6th day of hospitalization. In the middle group of patients, aged 65-84 years, 54.2% passed this goal by the 5th day. In the youngest group, 57.1% were ready to switch by the 4th day.

All told, the proportions of patients who met the criteria for switch therapy declined with age, going from 71% of the youngest group to 63% of the middle group to 56% of the oldest patients. The proportion of patients who were switched was similar across groups, however: 80% of the under-65 patients, 76% of the middle group, and 78% of those aged 85 and up.

After therapy was switched, the oldest patients were the least likely to require re-establishment of intravenous antibiotics. Just 2 (1.2%) of the 164 patients in the oldest group had to be switched back, compared with 20 (3.6%) of the 554 patients in the middle group and 46 (7.4%) of the 621 patients in the youngest group.

"The international cohort study of very elderly patients indicates that in this population, switch therapy is a clinically effective approach and facilitates an early hospital discharge," the investigators concluded. ■

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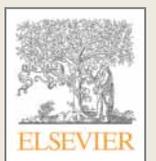
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Calfactant Improved Survival in Pediatric Lung Injury Trial

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

SAN DIEGO — Calfactant appeared to reduce mortality from acute lung injury in children, according to a study presented at the international conference of the American Thoracic Society.

Dr. Douglas F. Willson reported that 19% of children (15 of 77) treated with calfactant, a calf lung surfactant extract marketed as Infasurf, died during the 21-hospital study.

In contrast, 36% of children (27 of 75) in the placebo group did not survive. The odds ratio in favor of calfactant was 2.5.

The mortality advantage was a surprise to the investigators, who had failed to prove that calfactant would increase ventilator-free days, compared with a placebo.

Although the calfactant group had more ventilator-free days (13.2 days vs. 11.4 days) at 28 days, the difference was not statistically significant.

“We did find a very significant difference—honestly, frankly, and unexpectedly—in mortality,” said Dr. Willson of the University of Virginia Hospital in Charlottesville. “We did not know it until the data were completely analyzed.”

He emphasized that the findings of this randomized, controlled trial would have to be duplicated in a larger trial.

The study enrolled only half of its 300-patient goal and, therefore, was underpowered to prove its primary outcome or a survival advantage.

Whether calfactant decreases mortality “is open to question and needs to be tested again,” Dr. Willson said.

The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI), a network of clinical researchers from pediatric intensive care units, collaborated on the trial. Calfactant’s manufacturer, ONY Inc. of Amherst, N.Y., provided financial support.

Conducted over 3 years at 21 pediatric ICUs, the trial enrolled acute lung injury patients who had an oxygenation index of 7 or higher within 48 hours of ventilation. The average age of the children was 7.3 years, and the randomization produced two well-matched groups. Patients received 80 mL/m² of calfactant or placebo in two doses given 12 hours apart.

Among the conclusions offered by Dr. Willson were that calfactant produces acute improvement in the oxygenation index, as had been shown in previous stud-

THE MORTALITY ADVANTAGE WAS A SURPRISE, BECAUSE THE INVESTIGATORS FAILED TO PROVE CALFACTANT WOULD INCREASE VENTILATOR-FREE DAYS.

ies, and that intratracheal administration of calfactant is safe.

The main complications in the calfactant patients compared with the placebo group were hypertension (9% vs. 1%), hypoxia (12% vs. 3%), and bradycardia (3% vs. 1%). One child experienced atrial fibrillation that was reported to revert without therapy.

“Despite greater incidence of complications, there were no long-term effects, and no child was excluded from the study because of them,” Dr. Willson said.

The findings suggest that calfactant may be effective in direct lung injuries such as pneumonia and drowning, he added, but not in indirect lung injuries such as occurs with sepsis.

For the latter, there was no suggestion of any therapeutic effect with calfactant versus placebo, he said, adding, “One patient population might benefit from calfactant, and one patient population may not.”

A large, prospective, controlled, and blinded trial is being planned, Dr. Willson said, that will enroll more than 600 adult and pediatric patients with direct lung injuries at 25 participating centers.

The investigators need to determine which patients would benefit from treatment with calfactant, Dr. Willson said in an interview.

“If it were my kid, I would give them surfactant. There is no question,” he said, with the caveat that the available surfactants are “extraordinarily expensive,” costing as much as \$10,000 in an adult.

“It behooves us to figure out in whom it might work, so we are certainly not ready to say it saves lives,” Dr. Willson said. “There are very few proven therapies for ARDS [acute respiratory distress syndrome]. I think this has potential.”

CHANTIX™
(varenicline) TABLETS

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 justifies the potential risk to the fetus. **Nursing mothers.** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Labor and delivery.** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use.** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use.** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION, Special Populations, Patients with Impaired Renal Function). No dosage adjustment is recommended for elderly patients (see DOSAGE AND ADMINISTRATION, Special Populations).

Information for Patients:

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

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	3	3
Vomiting	1	1	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4

(Table 3 continued)

PSYCHIATRIC DISORDERS			
Sleep Disorders/Disturbances			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/TORACIC/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
Pruritus	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

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

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS.** **Infrequent:** Anemia, Lymphadenopathy. **Rare:** Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS.** **Infrequent:** Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. **Rare:** Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **EAR AND LABYRINTH DISORDERS.** **Infrequent:** Tinnitus, Vertigo. **Rare:** Deafness, Meniere's disease. **ENDOCRINE DISORDERS.** **Infrequent:** Thyroid gland disorders. **EYE DISORDERS.** **Infrequent:** Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. **Rare:** Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS.** **Frequent:** Diarrhea, Gingivitis. **Infrequent:** Dysphagia, Enterocolitis, Erection, 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:** Myostis. **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 abnormality, 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:** Exacerbation, 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.

How to Recognize CNS Manifestations of Tuberculosis

BY AMY ROTHMAN SCHONFELD
Elsevier Global Medical News

SAN DIEGO — Imaging plays a key role in determining whether tuberculosis is the cause of central nervous system symptoms that suggest cerebral infarction, disk herniation, prevertebral and epidural abscesses, para- or quadriplegia, headache, or photophobia, according to Dr. Richard F. Scafidi, who presented his findings as a scientific exhibit at the annual meeting of the American Society of Neuroradiology.

“Imaging can play a key role in not only aiding the diagnosis but recognizing the extent of the disease and its complications, and all of this will affect management,” Dr. Scafidi said.

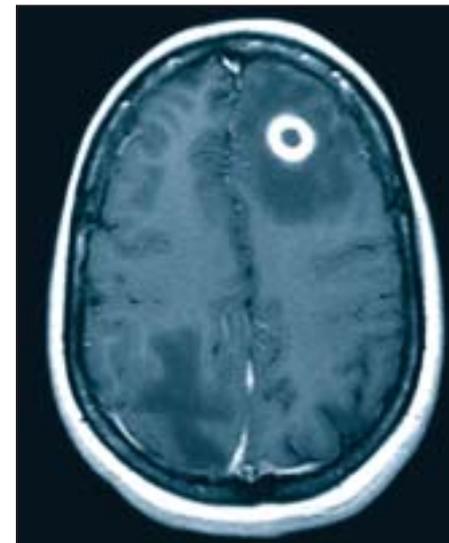
In 2004, 14,500 new cases of tuberculosis (TB) were reported in the United States, according to the Centers for Disease Control and Prevention. Although the overall TB case rate of 4.9 per 100,000 persons was an all-time low, TB continues to exact a toll on many communities here.

In the central nervous system, TB initially creates a subependymal or subpial tuberculous granuloma, known as a Rich focus, within the brain, spinal cord, or meninges. This infection focus can rupture into the subarachnoid space, causing

tuberculous meningitis and parenchymal tuberculomas. In the later stages of disease, leptomeningeal enhancement is seen; however, such findings may not be apparent early in the disease, said Dr. Scafidi, of the department of radiology at Robert Wood Johnson Medical School in Piscataway, N.J.

Parenchymal tuberculomas, with or without concomitant tuberculous meningitis, may be caused by hematogenous spread or dissemination into the cerebrospinal fluid infection after rupture of an adjacent Rich focus. Tuberculomas are typically found in frontal and parietal lobes, have multiple foci, and are associated with moderate to marked edema. On noncontrast CT, a tuberculoma looks like a noncalcified mass that may be rounded or lobulated with low or high attenuation. On contrast-enhanced CT a tuberculoma appears as a rounded, ring-enhancing lesion with a central area of low attenuation. MR with contrast allows differentiation of noncaseating from caseating (necrotic) granulomas. In this case, postcontrast MR demonstrated a rounded, well-circumscribed left frontal lobe lesion exhibiting both T1 and T2 hypointensity centrally with rim enhancement, indicative of a caseating granuloma.

Imaging techniques can also diagnose



A contrast-enhanced CT (left) reveals intracranial tuberculoma. The axial T1 weighted postcontrast MR image (right) shows intracranial tuberculoma.

PHOTOS COURTESY DR. RICHARD F. SCAFIDI

complications of tuberculous meningitis, including arteritis, infarction, and hydrocephalus. Arteritis most commonly involves the territory of the middle cerebral artery, basal ganglia, and internal capsule. Arteritis may lead to infarction and subsequent atrophy.

Disk herniation, compression fractures, prevertebral and epidural abscesses, and even para- or quadriplegia may result from

spinal involvement of TB, a condition known as tuberculous spondylitis or Pott's disease. Tubercular lesions may congregate around disks, beginning anteriorly in the vertebral body and spreading to subchondral bone, causing disk herniation into the vertebral body, disk destruction, or vertebral collapse with anterior wedging. Lesions can affect multiple levels within the upper lumbar and lower thoracic spine. ■

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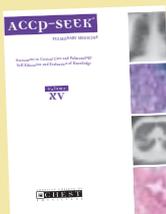
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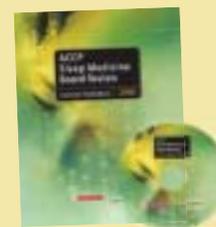
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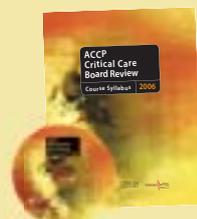
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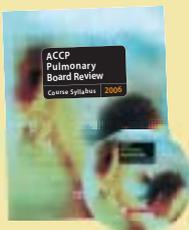
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NIH: Improve Access to Tobacco Cessation Programs

Numerous barriers block tobacco users from taking advantage of prevention and cessation therapies.

BY ALICIA AULT
Elsevier Global Medical News

BETHESDA, MD. — Tobacco cessation programs that employ telephone quit lines and counseling and nicotine replacement therapy are highly effective, and they should be offered to more smokers and users of smokeless tobacco, according to a panel of physicians, other health care providers, and community advocates at a conference on the prevention, cessation, and control of tobacco use sponsored by the National Institutes of Health.

The 14-member panel was charged with issuing a consensus statement on the state of the science after sifting through the available evidence and listening to several days of presentations from the public.

The NIH committee found ample evidence that tobacco-related illnesses are a huge burden in the United States—leading to 440,000 deaths each year—and also that there are many successful strategies for preventing use or helping people quit.

But there are huge and numerous barriers blocking tobacco users from taking

advantage of prevention and cessation programs, the committee added.

Of the 44.5 million adult smokers in the United States, 77% would like to quit, and 40% make an attempt in any given year, according to the panel.

But only 5% succeed, mostly because those attempting to quit cannot access effective treatments.

“To increase demand for treatments, we must motivate smokers to want them, expect them, and use them,” said Dr. David F. Ransohoff of the University of North Carolina at Chapel Hill, and chairman of the NIH panel, in a statement.

One of the biggest challenges is stopping people from starting.

The data show that most smokers begin in adolescence. Effective strategies to keep children from picking up the habit include raising taxes to increase cigarette prices, passing—and then enforcing—laws to prohibit minors’ access to tobacco, and creating smoke-free zones, said

the panel. Restricting tobacco ads and promotion and disseminating antitobacco mass media campaigns also work, the committee said.

“Tobacco is a legal product, but it’s illegal to sell that product to youth, so simply enforcing the law of not selling tobacco products to youth would help a great deal,” said panelist Stephen B. Thomas, Ph.D., director of the Center for Minority Health at the University of Pittsburgh.

PATIENTS AND PROVIDERS SHOULD BE MADE MORE AWARE OF THE BENEFITS OF CESSATION AND THE RESOURCES FOR QUITTING.

The committee also found that reimbursement for smoking cessation counseling or nicotine replacement products increased physician intervention and encouraged more patients to make use of the

services.

Patients also are more apt to seek out and use the services when discussions of smoking and quitting are made a routine part of every primary care visit or before every hospital discharge, the panel said.

There was some concern among anti-tobacco activists that the panel might endorse an idea making the rounds—that people trying to quit smoking could

reduce the level of harm by switching to smokeless tobacco. But the committee found limited evidence to support this notion and reiterated in their statement, “Use of any tobacco product must be discouraged.”

The committee also stated that people with psychiatric conditions—especially schizophrenia and major depressive disorder—are more likely to be smokers and to have a harder time quitting, with more severe withdrawal symptoms.

Going forward, patients and providers should be made more aware of the benefits of cessation and the resources for quitting, and reimbursement policies should be established, said the panel.

Its advice to tobacco users: “If at first you don’t succeed, try, try again and get some help,” said panelist Dr. Christine Laine of Jefferson Medical College, Philadelphia.

One antitobacco organization, the Campaign for Tobacco-Free Kids, said it was pleased with the panel’s deliberations and statement.

“For the most part, they hit all the major issues and, in our opinion, got most of it right,” said Matt Barry, director of policy research for the Washington-based campaign. ■

Copies of the consensus statement can be found at <http://consensus.nih.gov>.

Antiangiogenesis Drugs Move Ahead

Agents • from page 1

pulmonologists to look at the risk of bleeding and to look at cavitation,” Dr. Roy Herbst said in an interview after presenting a review of the new drugs and the state of antiangiogenic therapy against lung cancer.

“We need to find some sort of risk factors to stratify these patients,” said Dr. Herbst, of the department of thoracic/head and neck medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston, and the senior investigator of a series of lung cancer trials testing the combination of bevacizumab and erlotinib (Tarceva).

Dr. Herbst cited the survival advantages reported last year in a phase III trial combining bevacizumab with chemotherapy as well as early results from his study. “Despite these advances, few, if any, metastatic patients are cured,” he cautioned.

He called the three new agents “quite comparable” and noted that “signs of early activity are seen,” but cautioned that whether the new multitargeted tyrosine kinase inhibitors are more effective than single-targeted bevacizumab is “not clear yet” in non-small cell lung cancer.

Among the potential advantages of multitargeted agents, Dr. Herbst cited convenience, single-agent activity, the ability to act on both tumor and blood

vessels, and the potential to lower the cost of treatment.

He cautioned, however, that the inhibition of each target may not be equally effective with just one drug. Optimal combinations of more specific agents might be better, he said, warning also of the “potential for increased toxicity as one targets more receptors.”

Whether these agents can be used alone or should be combined with chemotherapy

or other targeted agents still has to be worked out in clinical trials, he said, calling for the assessment of biomarkers in future trials.

“I think angiogenesis inhibition has become a main-

stay in cancer therapy, and it will be very interesting in the next few years as we figure out how to optimize its use and use it safely,” Dr. Herbst said. “It is a perfect therapy to add to our existing methods.”

Sunitinib

Dr. Mark A. Socinski, FCCP, reported that sunitinib controlled tumor growth in more than half of 63 patients who had failed previous regimens for advanced non-small cell lung cancer.

Six patients (9.5%) had partial responses, and 27 patients (42.9%) had stable disease in the study. Median progression-free survival reached 11.3

weeks and overall survival 23.9 weeks.

Three patients died of hemorrhages, however: Two were pulmonary—only one of which was attributed to treatment—and one was cerebral.

Fatigue led the list of grades III and IV toxicity. Other adverse events in the trial included myalgia, neutropenia, stomatitis, headaches, and hypertension.

Patients received 50 mg of sunitinib daily for 4 weeks followed by 2 weeks off therapy before starting another cycle in the trial.

Dr. Socinski, director of the multidisciplinary thoracic oncology program at the University of North Carolina at Chapel Hill, announced that the study has been extended and 47 additional patients enrolled on a revised dosing schedule of 37.5 mg daily.

Sorafenib

Dr. Ulrich Gatzemeier reported that 30 (59%) of 51 patients with advanced non-small cell lung cancer had stable disease while they were treated with 400 mg twice a day of sorafenib. No partial responses were recorded in the study.

Another 18 patients (35%) progressed, and three patients died before they could be evaluated.

Median progression-free survival reached 11.3 months, and median survival 29.5 weeks. Two patients have been on therapy for 2 years, according to Dr. Gatzemeier, head of thoracic oncology at Grosshansdorf Hospital in Hamburg, Germany.

Four patients, all with squamous cell carcinoma, had tumor cavitation, and four patients had bleeding events. Three hemorrhages were described as minor, but a

fatal hemorrhage occurred in a cavitary lesion while the patient was receiving radiation therapy 30 days after stopping sorafenib.

Other adverse events included diarrhea, hand-foot syndrome, fatigue, and hypertension.

Dr. Gatzemeier announced that a phase III trial has already started. It is to randomize 900 patients to a carboplatin/paclitaxel regimen with sorafenib or a placebo.

ZD6474

Dr. Ronald B. Natale reported that 83 patients achieved a median progression-free survival of 11 weeks on 300 mg per day of ZD6474. In comparison, only 8.1 weeks was reached by a control arm of 85 patients treated with 250 mg of gefitinib (Iressa) daily. The response rates were 8% and 1%, respectively.

The trial allowed patients who had progressed to cross over to the other agent. There were no additional responses, but 16 of 37 patients who switched from gefitinib to ZD6474 achieved more than 8 weeks’ disease control vs. 7 of 29 patients who switched to gefitinib from ZD6474.

Overall survival, however, showed a trend in favor of starting on gefitinib: The median was 7.4 months vs. 6.1 months for those who began on ZD6474.

Adverse events included diarrhea, rash, asymptomatic QTc prolongation, and hypertension, but not hemoptysis.

Dr. Natale, a medical oncologist at the Cedars-Sinai Comprehensive Cancer Center in Los Angeles, concluded that the data support further investigation of ZD6474 as monotherapy. ■

‘MORE THAN EVER, WE NEED PULMONOLOGISTS TO LOOK AT THE RISK OF BLEEDING AND TO LOOK AT CAVITATION.’

New Trial Tests Sepsis Therapy

Low-Dose • from page 1

a 2006 Cochrane Collaboration systematic review of corticosteroids for treatment of severe sepsis and septic shock (Cochrane Library ISSN 1464-780X).

In 15 randomized trials totaling more than 2,000 children and adults included in the analysis, steroid therapy didn't change 28-day all-cause mortality. But the results varied according to dosing strategy. In nine trials of replacement-dose corticosteroids—the equivalent of hydrocortisone at 200-300 mg/day intravenously for 5 days or longer—there was a highly significant 20% reduction in the relative risk of 28-day mortality compared with placebo, along with a greater proportion of patients experiencing shock reversal by day 7. In contrast, patients on high-dose, short-course corticosteroids didn't benefit.

Several new trials have been published since completion of the Cochrane review. An updated analysis incorporating these studies shows a significant 12% reduction in all-cause mortality with steroid therapy when all trials are considered. Looking only at those involving low-dose therapy for at least 5 days, the relative risk reduction in mortality is now an even more robust 23%, he said.

The Cochrane review found no significant increase in rates of superinfection, GI bleeding, or hyperglycemia linked to steroid therapy, but Dr. Annane found those trial results inconsistent with real-world practice. These adverse events are common with steroids, he cautioned, adding that only patients likely to obtain therapeutic benefit should be exposed to such risks.

That's why American College of Critical Care Medicine guidelines, which were coauthored by Dr. Annane, recommend low-dose steroids only in septic shock that is refractory or accompanied by adrenal insufficiency, as defined by an increase in cortisol of 9 mcg/dL or less in response to a corticotropin test (Crit. Care Med. 2004; 32:1928-48).

The rationale underlying low-dose steroid therapy in septic shock is that systemic inflammation is a hallmark of sepsis. Inflammatory cytokines suppress the hypothalamic-adrenal-pituitary axis, resulting in adrenal insufficiency in roughly half of septic shock patients. Steroids induce immune modulation through numerous cellular mechanisms of action.

The indications for steroids in septic shock may soon increase. Dr. Annane is a leader of the 47-site European CORTICUS trial evaluating the impact of 5-11 days of low-dose hydrocortisone in a less severely ill population of septic patients than ever before studied. CORTICUS includes more than 500 patients with nonrefractory mild to moderate septic shock. The data are now being tabulated. ■

Dr. Curtis Sessler, FCCP, comments: *Many clinicians now routinely initiate corticosteroid therapy, typically hydrocortisone 200-300 mg per day, for patients who have septic shock that persists after fluid challenge. The Cochrane review lends substantial support that steroids hasten recovery from shock and reduce mortality. The good safety profile of this strategy documented in the Cochrane review is*

Is Combo Therapy Best in Septic Shock?

A key unresolved clinical issue regarding the use of corticosteroids in septic shock patients is whether the addition of fludrocortisone to low-dose hydrocortisone provides incremental benefit over hydrocortisone alone, Dr. Djillali Annane said.

"There is evidence of need for mineral corticoid supplementation in severe sepsis, and maybe what hydrocortisone provides is not enough," observed Dr. Annane.

Among the suggestive evidence is a recent 19-site prospective study involving 629 patients with septic shock.

The prescription of corticosteroids for patients in this observational study was at the discretion of the treating physicians.

Of the total, 163 patients received low-dose hydrocortisone, 249 patients received hydrocortisone and fludrocortisone, and 217 patients received no corticosteroids.

The patients in the three study groups were of similar age and disease severity.

Yet their death rates were strikingly different, with the best outcomes seen in those who were treated with

hydrocortisone plus fludrocortisone.

The findings of this observational study led to the launch earlier this year of an ongoing, multicenter, European randomized trial with a factorial design that is looking at the benefits and risks of combination steroid therapy, compared with hydrocortisone alone, Dr. Annane said.

Much of the interest in combination steroid therapy in septic shock stems from a French multicenter double-blind trial that Dr. Annane and his colleagues reported 4 years ago.

In that trial, the researchers randomized 300 adults with septic shock either to hydrocortisone IV at 200 mg/day plus a daily 50-mcg tablet of fludrocortisone, or to matching placebos.

The 28-day mortality was significantly lower in the combination steroid arm (JAMA 2002;288:862-71).

Ironically, the only reason fludrocortisone was included in the corticosteroid arm was that the study ethics committee insisted upon it, even though there was little evidence at the time to support that position, he recalled.

also encouraging but must be corroborated in future clinical trials. However, questions remain regarding the role of serum cortisol and corticotropin testing, duration of therapy and tapering strategies, and the role of

mineralocorticoids. The data regarding mineralocorticoids described by Dr. Annane are provocative, particularly for 1-month survival, but are not from a randomized clinical trial, and require additional scrutiny.

Critical Care Outreach Teams Target Hospital Obstacles

BY ALICIA AULT

Elsevier Global Medical News

PITTSBURGH — As more hospitals attempt to establish rapid response teams to handle decompensating patients, they often encounter entrenched cultures that may prevent the teams from proving their utility, several speakers said at a meeting on emergency response systems sponsored by the University of Pittsburgh Medical Center.

The teams go by different names: medical emergency teams (METs), rapid response teams, or critical care outreach teams. They are charged chiefly with trying to prevent cardiac arrest by intervening as early as possible. Typically, they are called when a patient is in respiratory distress, is hypotensive, has tachycardia, or has a change in consciousness.

However, the teams frequently are seen as a challenge to the established order, and they may be met with resistance, said Dr. Michael Buist, director of intensive care at Dandenong Hospital in Melbourne.

At Dandenong, a study showed that even when criteria existed

for calling a rapid response team, nurses did not make the calls in 17% of the episodes. This was partly because the nurses did not want to go against the established culture, he said.

At the University of California, San Francisco, Medical Center, the formation of a rapid response system was met with little enthusiasm, said Dr. Sumant Ranji, a professor of medicine. The hospital began a small rapid response program in mid-2005, rolling it out slowly by talking about it at monthly ward nurses' staff meetings, and through e-mails to physicians and announcements at house staff conferences.

Most of the coverage was during the day, by a team comprising a hospitalist, a second-year resident, and a clinical nurse-specialist. At night, coverage was by an on-call resident from the intensive care unit. Usage was low initially—about 1-2 calls per week, which amounted to 2-3 calls per 1,000 patients. This can be compared with the 25 calls per 1,000 patients seen with long-established programs at the University of Pittsburgh

Medical Center hospitals, for instance, Dr. Ranji said.

Reasons for underutilization of the rapid response team included a misperception about when the teams would arrive. During the education process, nurses and physicians were told to call the primary team first and then the rapid response team if there was no response or an inadequate re-

TO FACILITATE THE USE OF THE TEAMS, WARD STAFF ARE GIVEN LAMINATED CARDS THAT DESCRIBE THE TEAMS AND GUIDELINES FOR WHEN TO CALL.

sponse within an hour. They understood this to mean the team would not come at all until an hour had elapsed. They also believed if they called the team, the patient would definitely be taken to the ICU, he said.

Nurses were reluctant to break the chain of command, especially on surgical wards, he said. "This is not a culture that can change by one intervention,"

Dr. Ranji said. He also discovered that nurses and residents weren't calling the rapid response team because they made ample use of "curbside consults"—pulling ICU nurses or fellows aside in the hallway to get an informal opinion. "This might cut into our call rate for formal consults," he said.

There has been no change in the number of codes called or in the rate of in-hospital cardiac arrest or mortality, even though the response teams are now available 24 hours a day, 7 days a week, Dr. Ranji said.

As a result, the San Francisco university is questioning whether it is using the right model. The hospital is considering using an ICU clinical nurse-specialist or a nurse-practitioner as the point person for the teams in the hope that ward nurses will be more likely to call on these colleagues for help.

It's been smoother sailing at the 300-bed Allegheny General Hospital, a tertiary care facility for Drexel University, Philadelphia, which added MET coverage to its code team in the spring of 2006. The MET has a hospitalist,

ICU nurse, bed nurse, respiratory therapist, and intravenous team. The code team has a senior resident, ICU nurse, respiratory therapist, nurse-anesthetist or anesthesiologist, and senior surgical resident.

To facilitate use of the MET, ward staff are given laminated cards that describe the teams and guidelines for when to call them, Dr. Sharon Kiely, an internist at Allegheny, said at the meeting.

In March, there were 12 calls, 11 of which truly needed a MET; 46% of the nursing units had made calls. By April, there were 30 calls, 28 of which needed a MET. The numbers of calls were the same the following month, but 85% of the nursing units had made calls, Dr. Kiely said. Overall, 66% of the patients were transferred to a higher level of care, 26% were stabilized in their rooms, and the remaining 8% died.

Dr. Kiely said it appeared that the MET concept was well received. During meetings with house staff, almost all had agreed that it made sense, and there had been no complaints from nurses, she added. ■

Pulmonary Perspectives

Sarcoidosis: A Clinical Review

Sarcoidosis is a systemic granulomatous disease characterized by immunologic alterations that include depression of cutaneous delayed-type hypersensitivity, imbalance of CD4/CD8 T-cell subsets, an influx of T4 helper cells at the site of granulomatous activity, hyperactivity of B-cells, and the presence of circulating immune complexes. The initial reversible phase of the granulomatous inflammation is mediated by Th1 cytokine, while the fibrotic phase is modulated by biological response modifiers released by active macrophages that set the stage for re-

confer susceptibility to sarcoidosis (HLA DR 11,12,14, 15, and 17); whereas, there are other alleles that offer protection (HLA DR1, DR4, and possibly HLA DQ 0202).

Sarcoidosis commonly presents with bilateral hilar adenopathy with or without pulmonary infiltrates, reticulo-endothelial involvement, and ocular and skin lesions. Cardiac and central nervous system involvement are less frequent but more devastating. Because of the multisystem nature of sarcoidosis, patients with sarcoidosis often appear in the offices and clinics of general

practitioners, family physicians, internists, and practitioners of various specialties who then refer these patients to chest physicians, because the lungs are the most commonly affected organs. Thus, the burden of securing an accurate diagnosis and developing a therapeutic plan usually falls on the shoulders of pulmonologists (du Bois et al. *European Respiratory Monograph* 32. London: Maney, 2005; 64).

The Search

The diagnostic search starts with an awareness of the disease, followed by the following steps.

1. Recognize the clinical picture.

About 20 to 50% of patients complain of dyspnea, cough, chest tightness, or chest pain. Blurred vision, red-eye, photophobia, and loss of visual acuity occur in less than 20%. Lofgren syndrome, a combination of erythema nodosum and bilateral hilar adenopathy, is a manifestation of acute sarcoidosis. The combination of parotid gland enlargement, uveitis, and facial nerve involvement is called Heerfordt syndrome. Lupus pernio, the hallmark of chronic sarcoidosis, is often associated with bone lesions, chronic uveitis, and pulmonary fibrosis. Hypercalcemia is seen in about 10% of patients; whereas hypercalciuria is three times more common. Fatigue, polyuria, thirst, arthritis, heart block, mono- or polyneuritis, small nerve involvement, muscle weakness, or anemia may occur. Sarcoidosis is an iceberg syndrome, for many forms of the disease remain undetected (Fig. 1). The clinician must dig deep to uncover the latent forms of the disease.

2. Recognize the chest radiograph abnormality.

More than 90% of the patients have an abnormal chest radiograph. Conventionally, intrathoracic abnormalities are classified in four stages: stage 1, bilateral hilar or mediastinal adenopathy (BHL); stage 2, BHL with parenchymal infiltration; stage 3,

parenchymal infiltration without BHL; and stage 4, bullous, cystic, and emphysematous changes.

In about 5 to 10% of patients, the chest radiograph is normal, but, even in these patients, high-resolution chest computed tomograph (HRCT) may indicate characteristic abnormalities. CT scans can also detect additional mediastinal and thoracic nodes that are not visible on a chest radiographs. HRCT is helpful in assessing parenchymal abnormalities, including nodules along bronchovascular bundles (beading), particularly in the mid- and upper-lung fields, pleural or subpleural nodules, septal lines, confluent opacities with air-bronchograms, cystic or bronchiectatic lucencies, honeycombing, and bulla formation.

Despite the accuracy and availability of CT and HRCT, routine use of these tests in the management of sarcoidosis is neither necessary nor cost-effective. Magnetic resonance imaging (MRI) is helpful in evaluating the extent of damage in neurosarcoidosis and, to a lesser degree, in myocardial involvement (Mediwake et al. *Sarcoidosis. Lung biology in health and disease*. New York, NY: Taylor and Francis Group, 2006; 365).

3. Secure histologic evidence of noncaseating granuloma.

When confronted with a suggestive clinical and radiologic picture of sarcoidosis, it is important to obtain histologic confirmation. Fiberoptic bronchoscopy is the most helpful diagnostic procedure. Aspiration liver biopsy, not commonly used, is also a quick and convenient method to obtain histologic confirmation. If serial sections are cut throughout the biopsy, hepatic granulomas are observed in about two thirds of biopsies. Alternative sites depend upon the tissue involved. They include peripheral lymph nodes, skin, nasal mucosa, conjunctiva, lacrimal and salivary glands, muscle, and spleen. Biopsy specimens should be submitted for microscopic examination, culture, chemical analysis, and nucleic acid amplification (Teirstein et al. *Sarcoidosis Vasc Diffuse Dis* 2005; 22:139).

The histopathologic hallmark of sarcoidosis is a compact, round, or oval granuloma made up of radially arranged epithelioid cells with pale-staining nuclei. Lymphocytes found in the granuloma are usually seen at the periphery. The giant cell of the sarcoid granuloma may be of Langhan or of the foreign-body type. Caseation is absent. Minor degrees of fibrinoid necrosis

may be seen. Extensive necrosis, however, is rare. Asteroid, Schaumann, and Hamasaki-Wesenberg bodies are frequently found within the epithelioid and giant cells. The structural arrangement of the granuloma is an example of the perimeter defense seen in other infectious and noninfectious diseases; however, no single agent has ever been consistently shown or cultured from sarcoid granulomas.

4. Provide supporting diagnostic evidence.

New techniques, as they emerge, help to detect new features of the disease. When fluorescence angiography was introduced, it revealed leaking retinal veins. Serum angiotensin-converting enzyme levels and gallium scanning are helpful in monitoring the disease. HRCT and MRI scans have brought a new dimension to visualizing neurosarcoidosis. It is hoped that nuclear imaging and MRI studies will uncover latent myocardial sarcoidosis.

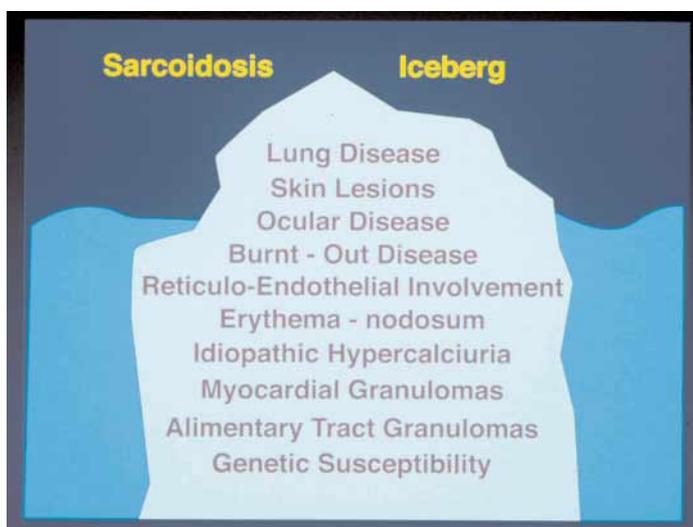
5. Do not overlook tuberculin testing.

The skin test result is negative in more than two thirds of patients with sarcoidosis. At the onset of the disease, a previously positive tuberculin test result becomes negative and, with cure, it tends to revert to its original responsiveness. A strongly positive tuberculin test is rare in sarcoidosis.

Therapy

There is no single cure for sarcoidosis. Corticosteroids are effective. The usual dose is 20 to 40 mg of prednisone daily for 6 to 12 months, gradually reduced to maintenance levels of 5 to 10 mg daily. Hydroxychloroquine is useful in chronic skin lesions, hypercalcemia, and neurosarcoidosis. Methotrexate, azathioprine, cyclophosphamide, and chlorambucil have been used. Thalidomide, pentoxifylline, mycophenolate mofetil, etanercept, and infliximab have been found effective in patients who do not respond to corticosteroids or who develop severe corticosteroid side effects (Baughman and Lower. *European Respiratory Monograph* 32. London: Maney, 2005; 301).

Om P. Sharma, MD, FCCP
Professor of Medicine
Keck School of Medicine
University of Southern California
Los Angeles, CA



modeling of lung tissue and inexorable fibrosis. Neutrophils, eosinophils, epithelioid cells, giant cells, and dendritic cells also participate. This drama is played in association with the class II major histocompatibility complex region of chromosome-6. What initiates the process remains unknown. Could unknown causative agents enter through the lungs? It would explain the presence of hilar adenopathy in more than 50% of patients with sarcoidosis. Even in the early stage, evidence of granulomatous spread can be found in the liver and lung (Hunninghake et al. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16:149).

The Patient

Sarcoidosis commonly occurs in the third and fourth decades of life. It is infrequent in children and the elderly. Cases in women outnumber those in men. Families with several members affected are common, because the likelihood of developing sarcoidosis ranges from 26 to 73% in individuals with a first-degree or second-degree family member with the disease. It is a genetically complex disease that involves not a single gene, but multiple genetic polymorphisms. There are several alleles that

Dr. Deborah Shure,
Master FCCP
Editor,
Pulmonary Perspectives

Dr. Aymar Robles, FCCP
Deputy Editor,
Pulmonary Perspectives

Editor's Insight

Sarcoidosis remains a disease of mysteries, despite years of research and clinical experience. Its cause or causes, reasons for remission, reasons for resistance to treatment, and best treatment remain open questions. This *Perspective* provides clinical insights for exploration of the iceberg of this enigmatic disease.

Hopefully, an increasing understanding of the genetics of this disease will shed light on future treatment options, in addition to the newer immunomodulatory treatments, including tumor necrosis modifiers, that are currently being investigated.

—Deputy Editor

NEWS FROM THE COLLEGE



BY DR. W. MICHAEL ALBERTS, FCCP

PRESIDENT'S REPORT Building a Sound Financial Future

I have just returned from the summer Board of Regents meeting and am settling in on the stretch run of my Presidency. I was particularly pleased with this year's summer meeting. It is traditionally devoted to the budget, and, as currently the one with the ultimate fiduciary responsibility, I am pleased to report that the College is in great shape.

I was especially pleased with the budget development process and budgeting philosophy. The document was prepared with input from many sources. In June, the Finance Committee reviewed the final document as synthesized by the executive staff and forwarded it to the full Board for review and approval. The budgeting philosophy employed utilized a conservative revenue projection but

outlined an aggressive programmatic agenda, all while predicting a positive bottom line (albeit minuscule). The College is a nonprofit organization and its mission is about education, not about making money, but we certainly can't lose money. A positive bottom line lets everyone sleep more soundly. On the flip side, the College is a service organization that exists to serve our members and their patients. We have a duty to use the funds to further our mission and vision. The approved budget accomplishes two important goals: providing a service to our members and ensuring that I sleep well at night.

Along the same lines, as a new initiative this year, an Audit Committee will be named, in addition to the Finance Committee. This committee will be charged with receiving and reviewing the yearly audit report. Following best corporate practices, the College has always had their "books" reviewed on a

yearly basis by an independent audit firm. This year, however, we have taken the next step and will form a separate Audit Committee. The five-person committee will be composed of the College treasurer, The CHEST Foundation treasurer, two Fellows of the College, and a nonmember with financial expertise. The Chair will be someone other than the Treasurers. Committee members will be named soon and will be charged with reviewing the report, including the

Management Letter. Based on this review, the committee will advise the Board of Regents through the Executive Committee on actions to be taken.

These are challenging times for medical societies, including the ACCP. Fortunately, the College is on sound financial footing, and, perhaps more importantly, one of the College's key competencies, developed over the years, has been an ability to adapt and even thrive during challenging times. ■

We Need Your Physician Assistant!

The ACCP is interested in recognizing the importance of the growing number of physician assistants (PAs) in the clinical workplace. We would like to assist PAs in advancing their knowledge in the medical and surgical subspecialty practices by having them join the ACCP as Allied Health

Members. Please help us and your PAs by recommending a PA for ACCP Allied Health Membership. Contact Cristina Vock, Membership Development Representative, at cvock@chestnet.org or (847) 498-8359, with the name and address of the PA you are recommending. ■

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ACCP to Welcome a New President

Dr. Mark J. Rosen, FCCP, will be inaugurated as the new ACCP President during Convocation ceremonies on October 22, during CHEST 2006.

Dr. Rosen is Chief of the Divisions of Pulmonary, Critical Care, and Sleep Medicine at North Shore University Hospital and Long Island Jewish Medical Center in New York, and Professor of Medicine at Albert Einstein College of Medicine. He received his medical degree from Brown University Medical School in Providence, RI. There, he was inspired to pursue a career in pulmonary medicine by his two faculty mentors: Dr. Richard Irwin, FCCP, and Dr. Sidney Braman, FCCP, both ACCP Past Presidents.

After his residency in internal medicine and fellowship in pulmonary medicine at Mount Sinai Medical Center, New York, NY, he completed a critical

care medicine fellowship at St. Vincent's Medical Center, also in New York.

Dr. Rosen is certified by the American Board of Internal Medicine in Internal Medicine, Pulmonary Disease, and Critical Care Medicine. He is a Fellow of the American College of Chest Physicians (ACCP), the American College of Physicians, and the Society of Critical Care Medicine.



DR. MARK J. ROSEN, FCCP

Dr. Rosen has been named repeatedly in the "Best Doctors in New York," "Best Doctors in America," and "Best Doctors in North America" listings. His research interests include pulmonary disease and critical illness in patients with HIV infection; and respiratory failure and medical ethics.

A nationally recognized educator, Dr. Rosen chaired the Scientific Program Committee for CHEST 1998, the annual international scientific assembly of the ACCP, and he was course director for

the ACCP Pulmonary Board Review Course from 1998 through 2001. He has published numerous articles and textbook chapters and co-edited the textbook, *HIV and the Lung*.

We asked Dr. Rosen for some insight into his upcoming presidential year:

Q: *What would you like to accomplish as President of ACCP?*

A: A 1-year term as President of the ACCP is not long, and my goals for that year should be lofty but not unrealistic. Like all of our ACCP Presidents, I would like to maintain our outstanding education and advocacy efforts in the face of increasing challenges, while providing all possible support to some outstanding new programs.

Q: *What do you consider to be the greatest strengths of the ACCP, and how will you build upon these during your Presidency?*

A: The College's greatest strength and its core mission has always been to improve patient care through education. Our educational efforts continue to expand and improve at a dramatic pace, and this progress must continue. Our journal, *CHEST*, has seen remarkable changes in the last year; under Dr. Richard Irwin's leadership as the new Editor in Chief, *CHEST* has a new look, a reorganized Editorial Board, and new editorial policies that have already resulted in a significant rise in the journal's impact factor. The annual international scientific assembly continues to deliver the best and most recent information valued by clinicians in the daily care of their patients. Future meetings will be enhanced by new hands-on experience with patient simulators to help clinicians learn new skills in airway management and ultrasound, and the College is embarking on a series of free-standing programs using this exciting technology. Finally, The CHEST Foundation will build on the Critical Care Family Assistance Program, smoking cessation programs, support of research, and philanthropic efforts around the world.

Q: *What is the greatest challenge facing the ACCP, and how will you address this challenge?*

A: The College faces many challenges, many of which can be grouped under a general category of increasing economic and regulatory constraints on delivery of care, on sustaining our educational programs, and on attracting the best people to pursue careers in our profession.

As the costs of care rise and budgets constrict, it will become increasingly difficult for us to fund the best possible care for our patients and to

maintain the workforce we need in all of the disciplines that work together in pulmonary, critical care, and sleep medicine. Our ongoing advocacy efforts with the American Thoracic Society, Society of Critical Care Medicine, and American Association of Critical-Care Nurses on addressing workforce issues must continue dynamically. New collaborative efforts must be pursued vigorously with Congress and payers to ensure that we will be able to provide the kind of care that we would want for ourselves and our families.

The costs of maintaining our educational programs continue to increase at the same time that our sources of funds are challenged by increasing scrutiny and criticism of industry sponsorship of these activities. Membership dues account for only around 18% of our annual revenues, and industry provides a great deal of support for our programs.

The College has already made great strides to ensure that our relationships with industry are transparent to our members and the public, while maintaining unimpeachable standards of ethical behavior. Industry sponsorship is always disclosed, and our revised Conflict of Interest Policy rigorously evaluates each proposed program and speaker for balance and scientific value.

Our procedures need to be evaluated almost continuously to ensure that these standards are upheld.

Finally, our patients and the payers rightly demand that we measure and disclose the quality of care we provide. However, clinicians are faced with increasing demands for these measurements, while lacking the tools to choose what to measure and how to measure it.

The ACCP has established a new Quality Improvement Committee to meet these challenges, and its work must be supported and expanded.

Q: *And finally, what is your charge to the members and new Fellows of ACCP?*

A: To members and new Fellows alike, in whatever role you play, I urge you to devote yourself passionately to patient-focused care as your first professional priority.

Providing this care as part of a team is also more effective than individual people and disciplines working independently and sometimes at cross purposes.

Despite the challenges and frustrations we all face dealing with agencies and institutions that often do not behave in ways that may best serve our patients and professions, I still believe that we do great work, and that our patients expect and deserve nothing less. ■

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NEWS FROM THE COLLEGE



EDUCATION INSIGHTS

How Will Quality Improvement Affect the Chest Physician?

BY SANDRA ZELMAN LEWIS, PHD
Research Specialist

Recent national efforts in quality improvement have been perceived by physicians in general, and chest physicians in particular, as a “runaway train that has left the station,” with the community of physicians trying to catch up with the train in the hope of influencing its future direction. Yet, the Institute of Medicine (IOM), which started this process when it published the landmark *Crossing the Quality Chasm*,¹ has a very different perception. In *Performance Measurement: Accelerating Improvement*,² the IOM calls for the quickened pace of improvement in quality of health care, less fragmentation, and more impact evaluation. As a result, the major players in performance measure development, endorsement, and implementation have pushed forward with hastened agendas and have

increased attention to the gaps in both the quality of care and the conditions in which performance measures are lacking. The ACCP Quality Improvement Committee (QIC) has been actively reviewing and voting on measures and standards submitted by the AMA Physician Consortium for Performance Improvement (AMA-PCPI) and by the National Quality Forum (NQF). The primary goal is for the QIC to help influence the design and content of these national efforts. Only measures and standards that cover pulmonary, critical care, and sleep medicine are selected for the committee to review, yet that has resulted in no less than one to three sets of measures per month. Upcoming timelines offer no hope of any deceleration, as the national effort is to implement measures to continue accelerating quality improvement initiatives at the local level and support pay-for-performance (P4P) initiatives at the national level.

For the chest physician, this means that as more performance measures are endorsed and implemented, there will be more pressure from hospitals and other institutions, as well as from the public and private payers, to meet these established targets for even more diseases, conditions, and situations. Pilot programs in value-based compensation or P4P are already in place in nearly every state, and plans are in place to convert many of those into standard payment practices. The Centers for Medicare and Medicaid Services (CMS) and many private insurers are planning to roll out compensation plans focused on the enhancement of quality health care in 2007. These P4P plans were originally to have been restricted to conditions in which measures are NQF-endorsed, but CMS and others have expressed dissatisfaction with the pace of the endorsement process.

Physicians should neither gain nor lose compensation for providing care to sicker or higher-risk patients. Most of the performance measures are process-oriented rather than outcome-oriented at this point. This continues to be an issue that is subject to discussion in many forums, including the ACCP QIC. Thus, whether or not physicians choose to treat sicker or higher-risk patients and regardless of the proportion of adverse outcomes among their patients, their compensation should only be based on whether the provided care was or was not the recommended treatment.

There are multiple other influences on your practice that emanate from the quality improvement movement in

American health care today. Some level of patient safety measures have been implemented in most of the hospitals today, but the drive for these changes has only been in existence since the IOM pointed out that *To Err Is Human*³ only 6 years ago. Quality improvement is the catalyst behind nationwide and local hospitals’ efforts to convert to electronic medical records. And, the American Board of Internal Medicine (ABIM), as part of its maintenance of certification (MOC) program, now requires applicants for recertification to participate in quality improvement efforts.

As the national quality improvement “train” continues to gain both momentum, the ACCP QIC is on board and partnering with the major national players to bring the latest and most relevant information to ACCP members. A highlight will be the CHEST 2006 Keynote Opening Session, an interactive discussion on “Quality Improvement, Performance Measures, and Pay for Performance: Why You Should Care.” Distinguished leadership from NQF, CMS, the AMA-PCPI, and the ABIM will participate in a panel discussion moderated by the current Chair of the QIC, Michael Baumann, MD, MS, FCCP. Please join us in Salt Lake City, UT, on Monday, October 23, 2006, at 1:00 PM, for this informative keynote presentation. ■

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1. Committee on Quality of Health Care in America, Institute of Medicine. *Crossing the quality chasm: a new health system for the 21st century*. Washington, DC: National Academy Press, 2001
2. Schroeder S. Committee on Redesigning Health Insurance Performance Measures, Payment, and Performance Improvement Programs. *Performance measurement: accelerating improvement*. Washington, DC: National Academy Press, 2006
3. Kohn LT, Corrigan JM, Donaldson MS. *To err is human: building a safer health system*. Washington, DC: National Academy Press, 2000



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Last-Minute Checklist

- ? **First and foremost—be there! October 21 – 26**
- ? **Bring your YELLOW registration packet with you** to the Express Registration Check-in at the Salt Palace Convention Center.
- ? **Don't miss Convocation and the Opening Reception** Sunday evening starting at 6:00 PM.
- ? **Plan to attend one or more NetWork meetings and special presentations.**
- ? **Still time to register** for one or more of the excellent **postgraduate courses** being held on Saturday and Sunday.
- ? **Schedule in these popular events**—check your final program for times and locations:
 - Daily literature review sessions
 - Simulation education in Ballroom B in the convention center
 - Keynote session
 - Curriculum-based learning sessions
 - Poster grand rounds audio tours
 - Practice management roundtable discussions
 - CHEST Challenge Playoffs (Mon/Tues/Wed) and Championship (Wed evening)
 - Walk/Run for Lung Health (Tues)
 - Poster Best-in-Category Awards (Wed evening)
- ? **Free Food!** Complimentary lunch will be served in the exhibit hall Mon-Wed. Most satellite symposia offer complimentary breakfast or dinner before their events—choose from sessions on Mon and Tues mornings and evenings and Wed morning; Affiliate luncheon on Mon; Women's NetWork luncheon on Tues; and Cultural Diversity in Medicine luncheon on Wed.
- ? **Check the Ambassadors Group events...**listed in your final program.
- ? **Stop by ACCP Central—we're at your service!** ACCP staff on hand to answer all your questions about the ACCP, The CHEST Foundation, NetWorks, and Institutes.
- ? **Shopping's the name of the game at the famous ACCP Bookstore.** Featuring the newest ACCP-SEEK XVI—Critical Care Medicine; 2006 Pulmonary, Critical Care, and Sleep Board Review syllabi; and many more educational values and ACCP logo items.
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New User-Friendly Tools To Build Career Connections

The official online job bank of the ACCP is now offering new features. Career Connection recently launched new, user-friendly components, allowing members even easier access and exposure to career advancement opportunities.

New features include an easy-to-use Resume Builder, where members create and customize resumes by means of a template. Career Connection now allows for the uploading and storing of existing resumes. Also, the new My Site section allows members to build their own password-protected

Web site, complete with unique Web address and personalized homepage. As always, members are still provided the opportunity to receive e-mail job alerts. All ACCP members are welcome to join. Features are free to job seekers and supply instructions and templates.



Need to fill a position? Employers can also take advantage of Career Connection by posting job openings, for a fee. Visit www.chestnet.org, and click on the Career Connection icon. Visit Career Connection in ACCP Central at CHEST 2006. ■

You Can Make a Difference As an Ambassador

BY DEBRA ALBERTS
 Chair, Ambassadors Group

I joined the Ambassadors Group at its inception. It seemed like such a great idea. I was already passionate about the work my husband was doing with the ACCP, so why not join the Ambassadors Group of The CHEST Foundation. Like most of you, I was already involved with many volunteer organizations at home, but I thought, "Why not support my spouse and his professional organization?"

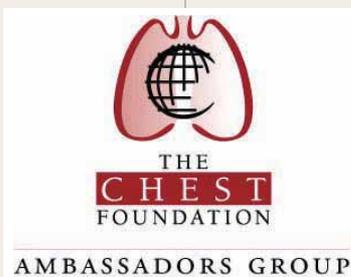
Over time, I was inspired about the work and by the wonderful individuals I met. I became convinced that the work of the Ambassadors Group in support of The CHEST Foundation could make a difference. I invite you to become a member of the Ambassadors Group and become personally passionate about the group and the good works they do.

The Ambassadors Group offers many wonderful resources online to help you explore your interests and find your niche. In doing so, you will learn ways to effectively act as emissaries and health advocates for the ACCP and The Foundation. For example, by going to www.chestfoundation.org, you can browse and even download the Women & Girls, Tobacco, & Lung Cancer Speaker's Kit. Plus, there are many other choices offered for educating children and for leadership training. These in-

credible free educational resources can interest individuals in adopting our programs or enhancing a lung health program already in place.

A number of additional resources are available in the ACCP catalog, which is also accessible online. The "Love Your Lungs" wristband campaign has been a tremendous success. By selling or gifting these wristbands to pediatricians and pediatric pulmonologists, you are serving as health advocates and helping to fund future lung health programs. The booklet series, *Stories at the End of Life*, may be ordered from the catalog. By contacting local hospitals, hospice centers, and libraries, the distribution of these powerful stories may assist patients and families at crucial points in life's journey.

These are just a few of the ways you can become involved. It is not only gratifying to promote The CHEST Foundation and the wonderful work they do, but you are making lifelong friends. Please feel free to contact the Ambassadors Group through our ACCP staff liaison, Sandy Lewis, at slewis@chestnet.org, or for more information, go to www.chestfoundation.org. ■



Reaching Out Makes a Lasting Impact on Students

BY SUSAN KVALE
 Immediate Past Chair

I would like to express my sincere thanks for your efforts on behalf of our students at Sycamore Canyon Elementary School. I truly think that the information you presented to them had a great impact on them, and I have no doubt this impact will affect their decisions later in life. How can we possibly thank you for that? My class is still talking about your presentation! They loved your visuals (especially the jar of tar), your easily understood way of explaining things, the fact that you engaged them during the presentation, and your friendly manner. In a nutshell, it was terrific."

The quote above is an excerpt from a letter written to me by teacher Lynne Baker, after I presented two sessions (90 students) on the Dangers of Smoking on a recent trip to San Diego while we attended the annual meeting of the American Thoracic Society.

After I received this letter of thanks, it makes me more determined than ever before to continue my efforts

and urge all ACCP members to reach out and get programs started in their communities. Together, we can all make a difference! Just think of the lives we can save if each of us teach the future generations to love their lungs! The kids are listening; we just need to be willing to get the facts out there for them to hear. Here are a few comments from the kids:

"You really made a difference to all who were listening. I know now that I will never smoke and my lungs will not be black."

"I never knew smoking kills so many people. What you told me is stuck in my brain forever."

"I never knew there were so many harmful chemicals in cigarettes. Someday, I can be a better parent because I can teach my child the dangers of smoking."

I could go on and on with comments, but now you know they are listening. Let's all move forward and expand our efforts to educate children about the dangers of tobacco and not to smoke. ■

For more information or to learn more about the Ambassadors Group tobacco prevention programs, go to www.chestfoundation.org or contact Sue Ciezadlo, sciezadlo@chestnet.org.

Operation Aftershock: ACCP Member Delivers Earthquake Relief

BY CAPT DENNIS E. AMUNDSON,
 MC, USN, FCCP
 ACCP Disaster Response
 Steering Committee Member

At 0600 on May 27, 2006, the people of Yogyakarta City and Bantul and Central Java Provinces, Indonesia, were severely affected by a devastating 6.3 Richter scale earthquake.

Within 2 days following the earthquake, a contingent from Third Marine Expeditionary Brigade Okinawa, Japan (3D MEB), arrived in Yogyakarta, Indonesia, in direct support of Humanitarian Assistance/Disaster Relief (HA/DR) mission named "Operation Aftershock." On May 31, Commodore B. Martin and CAPT J. Moore of the USNS MERCY responded to Indonesian and Department of Defense (DOD) requests for further assistance in the earthquake by deploying a four-person MERCY medical team composed of one critical care physician, one pediatric specialist, a public health physician, and a family practice provider to support the HA/DR response mounted by 3D MEB.

By the third day after the earthquake, the augmented 3D MEB with 22 medical staff

composed of physicians, nurses, and corporal staff had begun medical, surgical, and public health services to the earthquake victims within its area of responsibility, the badly damaged province of Bantul.

From May 31 to June 14, 3D MEB provided over 3,500 tetanus and 300 childhood measles immunizations, as well as performed medical and surgical services to almost 4,000 earthquake victims. Several disease outbreak investigations were performed, and a variety of public health education programs were presented for the local and provincial population. Thirty cases of water treatment solution were selectively distributed for control of water-borne outbreaks. Extensive family/civilian training was employed for posttrauma wound care and for fracture care and self-aid for the follow-up period.

This evolution in planning and implementation was deemed a huge success and could serve as the model for further DOD HA-DR. ■

DR. AMUNDSON is Program Director, Pulmonary/Critical Care, Naval Medical Center, San Diego, CA; and Associate Professor of Medicine, Uniform Services University, Bethesda, MD.

Corpus Christi Member Raises \$32,000 for Antitobacco Campaign

BY DR. KAY
 GUNTUPALLI, FCCP,
 AND DR. STEPHANIE
 LEVINE, FCCP

Dr. Salim Surani, FCCP, a private practice pulmonologist in Corpus Christi, TX, has devoted significant time and effort to bringing The CHEST Foundation's anti-tobacco campaign to the local schools in his area. His efforts have resulted in generous donations made to The Foundation in support of this project from many hospitals and physician groups in the vicinity, including:

- ▶ \$15,000 from Christus Spohn
- ▶ \$10,000 from Kindred Corpus Christi
- ▶ \$5,000 from Coastal Cardiology
- ▶ \$1,000 from Torr Sleep Center
- ▶ \$1,000 from Corpus Christi Heart Foundation.

On June 23, the local media and press held a press conference to honor the donors and Dr. Surani. Dr. Kay Guntupalli, FCCP, a former member of the Board of

Trustees of The CHEST Foundation and designer of the anti-tobacco DVD and animated cartoon book for children, and Dr. Stephanie M. Levine, FCCP, a member of the Board of Trustees of The CHEST Foundation, were on hand for the event. The medical community spoke about the importance of this medical-community educational initiative. The event was enthusiastically covered by television and print media.

Using the "AntE Tobacco" tool kit for children developed by Dr. Guntupalli for The CHEST Foundation (cartoon CD, cartoon book, coloring book), Dr. Surani educated 1,000 grades 2, 3, and 4 children in Corpus Christi. He has assembled volunteers who are passionate about the cause. Data are being collected on the baseline knowledge and the ability to understand and retain the message given by the program. The monies raised will help reach an estimated 25,000 school children in the next school year. ■

NEWS FROM THE COLLEGE



What To Know Before You Go

That's right. CHEST 2006 is just around the corner. First, check out new Delta Air Lines discounts at www.chestnet.org/CHEST/program/hotel.php.

Next, here are a few tips to help you hit the ground running.

Once you touch down, from the airport, you can catch a cab or hop a bus for just a few dollars. Or, check with your hotel—some offer transportation services of their own. On site, CHEST 2006 provides complimentary shuttle buses to transport guests between the hotels and the convention center.

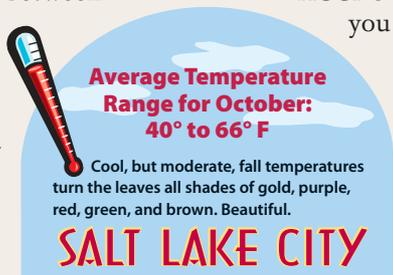
Upon arriving at the Salt Palace Convention Center, all guests must report to the ACCP registration area for check-in. For faster service, preregistered guests should

bring their yellow registration packet to the express check-in counter. You can avoid the lines during peak times by taking advantage of the extended registration hours.

The Salt Palace Convention Center is in the heart of downtown. Awe-inspiring views can be witnessed from all sides, and the inviting terrain is easy to explore thanks to free public buses and the TRAX-light rail service. Combine all of this with the educational and networking opportunities offered during the

ACCP's annual meeting—and you just can't go wrong.

Salt Lake City! It's the perfect reason to arrive early to CHEST 2006 or to stay late. Visit www.visitsaltlake.com or www.chestnet.org/CHEST for more details.



Patient Education Organization NATT Supports Education on DVT, Pulmonary Embolism

BY LORI PRESTON, MBA
NATT Vice President

The National Alliance for Thrombosis and Thrombophilia (NATT) is a nationwide, community-based, nonprofit, volunteer, health organization that was formed in August 2003. In keeping with our goal to ensure that people suffering from thrombosis and thrombophilia receive early diagnosis, optimal treatment, and quality support, we have many initiatives underway for 2006.

On May 9, 2006, the Surgeon General of the United States, Vice Admiral Dr. Richard H. Carmona, spoke at the conclusion of a 2-day workshop on deep venous thrombosis and pulmonary embolism and committed to issue a *call to action* to pre-

vent and decrease the tremendous negative impact of deep venous thrombosis and pulmonary embolism on the American public.

We at NATT are committed to working aggressively and tirelessly to build on the momentum of the Surgeon General's *call to action*.

NATT offers resources that can be used as educational handout materials for inpatients and outpatients. At our Web site, peer-reviewed PDF files and brochures on thrombosis- and thrombophilia-related topics, newsletters, and information about our patient education seminars can be downloaded. These can be accessed at www.nattinfo.org/learn-resources.htm.

Contact Lori Preston via e-mail at lpreston@keelan.com.

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SLEEP STRATEGIES

The IOM Sleep Report: Implications and Opportunities

In May, the Institute of Medicine (IOM) released its report on sleep disorders and sleep deprivation.¹ IOM reports can have profound impact on the practice of medicine. For example, the IOM publication, *To Err Is Human*² is often credited with jump-starting the modern field of patient safety. Chest physicians have a significant stake in the field of sleep medicine (called *somnology* in the report; the only place I have heard that term used). A majority of those who are board-certified in sleep medicine are pulmonologists, and a majority of both accredited and nonaccredited sleep laboratories are directed by pulmonologists. We are very often the first point of contact for the patient with suspected sleep-disordered breathing, and many of us have learned about the gamut of sleep disorders along the way. Therefore, the IOM report is relevant to many chest physicians.

The IOM report makes 10 key recommendations:

1. The National Center on Sleep Disorders Research (NCSDR) and its advisory board should play a more proactive role in stimulating and coordinating the field. Since the publication of the report, its new acting director, Dr. Michael Twery, has seemingly been everywhere at once, prodding, encouraging, supporting, and recruiting sleep investigators. It should be noted that the entire staff of the NCSDR is less than two full-time employees. The Advisory Board of the NCSDR has a new chairman, Dr. Phyllis Zee, who is a neurologist and important contributor to the 2006 ACCP Sleep Medicine Board Review course.
2. The National Institutes of Health and private foundations must increase investment in interdisciplinary somnology and sleep medicine research training and

mentoring activities. The ACCP, which probably includes one of the largest collections of sleep medicine practitioners and scientists, has a role to play here.

3. The National Center on Sleep Disorders Research and the Centers for Disease Control and Prevention (CDC) should establish a multimedia public education campaign. Indeed, such a campaign is being developed, and the ACCP is part of it. Based on the highly successful Colorectal Cancer Screening Roundtable, the CDC and the National Sleep Foundation (NSF) have developed the National Sleep Awareness Roundtable (NSART). The ACCP Sleep Institute is a founding member of NSART.

4. Centers for Disease Control and Prevention and the National Center on Sleep Disorders Research should support additional surveillance and monitoring of sleep patterns and sleep disorders. The NSART working agenda includes surveillance research. Through NSART, ACCP will be able to contribute to framing the questions and methodology to be employed by the group at large.

5. Academic health centers should integrate the teaching of somnology and sleep medicine into baccalaureate and doctoral health science programs, as well as residency and fellowship training and continuing professional development programs. The ACCP has been a leader in professional development programs for sleep clinicians. First is its longstanding sleep medicine course (now directed by Dr. Jim Parish, FCCP). By the time

you read this, the ACCP will have completed the presentation of its first Sleep Medicine Board Review course. Further, the ACCP Sleep Institute is developing a curriculum for a regional sleep seminar series to be offered in ACCP members' sleep laboratories for the primary care physician.

6. Develop and validate new and existing diagnostic and therapeutic technologies. This recommendation gets to the heart of the portable monitoring debate, which is a long and disturbing

story. The report revisits the prevalence and consequences of untreated sleep disorders and notes the "cumbersome nature

and cost of the diagnosis and treatment" of these problems. Since the most prevalent and dangerous of sleep disorders is sleep apnea, which is the bailiwick of pulmonologists, we need to consider taking a leadership role in advocating for more cost-effective methods of diagnosis and treatment.

7. Expand accreditation criteria to emphasize treatment, long-term patient care, and chronic disease management strategies. The IOM report takes the current American Academy of Sleep Medicine (AASM)-administered sleep laboratory accreditation process to task in this regard, noting "... the primary focus of most existing sleep centers appears to be on the diagnosis, rather than on comprehensive care of sleep loss and sleep disorders as chronic conditions. This narrow focus may largely be the unintended result of compliance with criteria for accreditation of sleep laboratories, which emphasize diagnostic standards and reimbursement for diagnostic testing. To address this, it is recommended that accreditation criteria for sleep centers, in which are imbedded sleep laboratories, be expanded to emphasize treatment, long-term patient care, and management strategies." The ACCP has already taken steps to develop processes for patient-centered care. In early September, the ACCP Sleep Institute will host an Obstructive Sleep Apnea Continuity of Care Conference, bringing together stakeholders to begin the process of developing guidelines for the long-term care of patients with sleep apnea.

8. It is recommended that the National Institutes of Health establish a National Somnology and Sleep Medicine Research Network. It will be up to the membership and leadership of the ACCP to decide whether to include such an initiative in our advocacy agenda.

9. The National Institutes of Health should ascertain the need for a trans-disciplinary sleep laboratory that would serve as a core resource in its intramural clinical research program. Again, the membership and leadership of the ACCP will need to decide whether to include such an initiative in our advocacy agenda. A natural partner in this and related endeavors would be the American Thoracic Society.

10. New and existing sleep programs in academic health centers should conform to meet the criteria of a Type I, II, or III interdisciplinary sleep program. According to the criteria in the IOM report, a Type I program offers educational programs for medical students and residents in primary care. A Type II program also provides education, training, and research in sleep medicine and includes an accredited sleep fellowship program. A Type III program does all that Types I and II do but also acts as a regional coordinator for a proposed research network. The IOM report tasks the AASM with developing accreditation criteria for sleep programs specific to academic health centers. On its Web site, the AASM responds in part, "Currently, research and financial policy for most sleep centers and academic units are not controlled by those units but rather by other agencies and departments ... For academic sleep centers, this would require establishing sleep medicine divisions or departments."³ Setting up fiscally independent academic units of sleep medicine is a laudable but probably unrealistic goal. In this regard, it is worth noting that a majority of academic sleep programs are housed in divisions of pulmonary medicine and that there are concerns about the current AASM-directed accreditation process for sleep centers (see #7 above).

The IOM report is quite relevant for chest physicians and the ACCP.

The IOM report scrutinizes the current state of clinical practice and research in sleep medicine and finds many significant problems that need to be addressed. Since sleep medicine is now part of the practice of pulmonary medicine, the IOM report is quite relevant for chest physicians and the ACCP.

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Sleep Institute

American College
 of Chest Physicians

This Month in CHEST: Editor's Picks

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



- ▶ Evidence of Innervation in Talc-Induced Pleural Adhesions. Dr. Juan F. Montes, et al
- ▶ A Comparison of Cytology and Fluorescence in Situ Hybridization for the Detection of Lung Cancer in Bronchoscopic Specimens. Dr. Kevin C. Halling, et al
- ▶ Inhaled Corticosteroids and Mortality in COPD. Dr. Christine Macie, FCCP, et al
- ▶ How Frequently Is Venous Thromboembolism in Heparin-Treated Patients Associated With Heparin-

Induced Thrombocytopenia? Dr. Robert L. Levine, FCCP, et al

- ▶ Abnormalities on Chest Radiograph Reported in Subjects in a Cancer Screening Trial. Dr. Paul F. Pinsky, et al

- ▶ Pulmonary Practice Profiles: Results of a Practice Performance Survey. John S. Bauer, FACMPE, et al

- ▶ Goodbye Ghostwriters! How To Work Ethically and Efficiently With Professional Medical Writers. Dr. Karen L. Woolley

- ▶ Gene Therapy for Pulmonary Diseases. Dr. Martin Kolb, et al

www.chestjournal.org

NEWS FROM THE COLLEGE



NetWorks: New Speaker's Kit and CHEST 2006 News

Affiliate

CHEST 2006 will feature a variety of sessions and programs of particular interest to ACCP physicians-in-training. The case report sessions will highlight 144 abstract presentations. The presenters are all affiliate members of the College. They will each discuss a unique case, followed by an expert who will provide further comments. In addition, nine teams have been selected to participate in the CHEST Challenge. This annual Jeopardy-style competition provides a unique learning experience for all participants and attendees. All affiliate members and training program directors are encouraged to attend the Affiliate NetWork Luncheon and Open Meeting on Monday, October 23, at 11:30 AM. E-mail your ideas anytime to the NetWork Chair, Dr. Brian Carlin, FCCP, at bcarlin@wpahs.org.

Airways Disorders

At CHEST 2006, the Airways Disorders NetWork Open Meeting on Monday, October 23, at 8:15 AM, will feature a presentation by Dr. Paul L. Enright, Using Spirometry To Screen for COPD: Is It Effective? What Are the Risks and Benefits? The asthma, COPD, and cystic fibrosis subcommittees of the NetWork are requesting input for new project ideas. Ongoing projects include the following:

- Disseminating information to assist ACCP members in the transition to non-CFC inhalers.

- Further developing the joint NetWork project on inhaled aerosol devices to include handouts for the use of non-CFC inhalers. The existing patient education handouts will be available on CD-ROM, as part of the ACCP Asthma Toolkit.
- Involvement in the ACCP Sleep Institute, asthma guidelines, and the triennial World Asthma Meeting.

Contact the NetWork at networks@chestnet.org.

Allied Health

With health-care dollars becoming scarce, diversification of revenue streams allows a strategic edge. The Practice Management Department has produced a yearly ACCP best seller, *Appropriate Coding for Critical Care Services and Pulmonary Medicine*. The Sleep Medicine and Allied Health NetWorks are contributing their expertise to chapters in the 2007 edition of the book. The chapter in last year's manual on sleep medicine will be expanded to include sleep-related durable medical equipment. This edition will highlight the processes to start dispensing continuous positive airway pressure and disposable supplies from a sleep center. Information will include guidelines for appropriate reimbursement. Information is available at www.chestnet.org/practice/pm/codingBook.php.

Cardiovascular Medicine and Surgery

The NetWork would like to welcome two surgeons as new steering committee

members: Drs. G. Hossein Almassi, FCCP, and Wickii Vigneswaran, FCCP. Dr. Almassi is a cardiothoracic surgeon at the Medical College of Wisconsin, with focus on aortic surgery and surgery for arrhythmias—especially atrial fibrillation and beating heart surgery. Dr. Vigneswaran is an actively practicing thoracic surgeon in academic practice at the University of Chicago. His interests are in minimally invasive lung surgery and heart/lung transplantation, and his research interests are new technology, outcomes, and studying lung injury. The NetWork will be showcasing excellent sessions at CHEST 2006, including the NetWork Open Meeting topic, Cells and Genes: The Next Wave of Cardiovascular Therapeutics. Please join us at our NetWork Open Meeting on Wednesday, October 25, at 8:15 AM.

Chest Infections

Safety Concerns for Two Antibiotics
By Dr. Kelly A. Wood, MHS, FCCP

The association of telithromycin with hepatotoxicity and gatifloxacin with dysglycemia raises concerns among chest physicians prescribing these antibiotics for respiratory infections. Telithromycin is the first ketolide antibacterial agent approved by the Food and Drug Administration (FDA). Three previously healthy patients who developed severe hepatotoxicity within a few days of taking telithromycin have been described (*Ann Intern Med* 2006; 144:415). One patient required orthotopic liver transplantation, and one patient died. Histologic examination in these two cases showed massive hepatic necrosis, consistent with drug-induced injury. Additionally, the FDA's Adverse Event Reporting System describes 10 cases of hepatic adverse events associated with telithromycin, ranging from serious to fatal.

The postmarketing period also disclosed reports of serious disturbances of glucose homeostasis with gatifloxacin. A population-based, nested, case-control study of patients 66 years and older showed that gatifloxacin was associated with an increased risk of hypoglycemia (adjusted odds ratio, 4.3; CI, 2.9 to 6.3) and an increased risk of hyperglycemia (adjusted odds ratio, 16.7; CI, 10.4 to 26.8), as compared with macrolide antibiotics (*N Engl J Med* 2006; 354:1352). Some reported dysglycemic events have resulted in fatal outcome. Recently, Bristol-Myers Squibb announced that it would cease production of its formulation of gatifloxacin. However, other formulations remain in areas of the world.

Clinical Pulmonary Medicine

Mesothelioma: A Brief Update

Malignant pleural mesothelioma (MPM) remains a major therapeutic challenge. A controlled study of surgery vs best supportive care is

underway in the United Kingdom, but uncontrolled data continues to make treatment choices largely subjective. Survival averages 6 to 12 months, but untreated patients have lived up to 14 years, with an 8% 5-year survival. Medical thoracoscopic talc poudrage (TTP) resulted in a 19-month median survival (mean 24) for MPM presenting with pleural effusion (Aelony et al. *Respirology* 2005; 10:649). Surgical resections produced a 34-month survival with early-stage disease (Rusch et al. *J Thorac Cardiovasc Surg* 2001; 122:788). The best centers report 4 to 11% 30-day mortality after surgery with major morbidity in 30 to 50% of patients and no cures. Chemotherapy with platins and antifolates improved survival by over 2 months, compared with platins alone, but quality of life declined during therapy (Bottomley et al. *J Clin Oncol* 2006; 24:1435). Radiation therapy provided good control of local outgrowths, but fails to stop disease progression. Indwelling catheters may relieve fluid pressure and dyspnea but deplete body protein and lymphocytes; reported survivals are shorter than TTP (Tremblay et al. *Chest* 2006; 129:362). Promising future approaches include immunotherapy and gene therapy.

Cultural Diversity in Medicine

Each year, the Cultural Diversity in Medicine NetWork provides a number of excellent programs at the annual CHEST meeting. The NetWork would like to draw your attention to two first-time events scheduled at CHEST 2006. Culturally competent health professionals are the key to eliminating racial and ethnic disparities in health care. A postgraduate course, Culturally Competent Health Care: An Education Program for Chest Physicians, will take place on Sunday, October 22. CHEST 2006 coincides with Eid-ul-Fitr, a celebration by Muslims on the first day of the month, following the end of the month of Ramadan (fasting). The ACCP, through the Cultural Diversity in Medicine NetWork, will host the Eid-ul-Fitr prayer for Muslims attending CHEST 2006.

Members in Industry

Ever wondered if you are an entrepreneur? The Members in Industry NetWork Highlight session, I have an Idea for a New Medication, Technology, or Company: What Do I Do? will be presented at CHEST 2006 on Monday, October 23, at 8:30 AM. The Members in Industry NetWork is also presenting a postgraduate course and two additional NetWork Highlights at CHEST 2006.

Sleep Medicine

The Sleep Medicine NetWork continues to move forward, promoting sleep medicine as a specialty, providing



educational and research opportunities, and raising awareness of issues pertinent to the practice of sleep medicine. An educational slide kit on sleep disorders is currently being developed as a resource that pulmonary physicians can use when giving lectures on sleep medicine topics to the general medical community. The NetWork is also involved in a variety of joint activities with the ACCP Sleep Institute, such as the Regional Sleep Training Programs for primary care physicians. Those who would like to learn more about the NetWork are encouraged to attend the open meeting at CHEST 2006, scheduled for Tuesday, October 24, 2006, at 8:15 AM. Dr. Bhargavi Gali, FCCP, will present the topic Preoperative Screening for Obstructive Sleep Apnea.

Women's Health

By Dr. Janet Myers, FCCP

The Women's Health NetWork is pleased to announce a new CD-ROM "Speaker's Kit" for tobacco prevention and cessation, "Make the Choice: Tobacco or Health?" The kit will include more than 200 PowerPoint slides full of new information. Other special features include new sections on gender influences on COPD and on lung cancer, information on the effects of passive smoke, recent data on noncigarette and smokeless tobacco products, a section just for girls, and updates on tobacco cessation medications, public policy, and the effects of the Tobacco Master Settlement Agreement. The Women's Health NetWork Speakers Kit Revision Committee is co-chaired by Dr. Janet Myers, FCCP, and Dr. Marilyn Glassberg, FCCP. Make the Choice: Tobacco or Health? will be unveiled at the Women's Health NetWork Luncheon at CHEST 2006. Please contact Marilyn Lederer at mlederer@chestnet.org.

Please access the CHEST 2006 advance program at www.chestnet.org for information on NetWork Highlights and other NetWork sessions.

Practice Management Update: Medicare Changes

Medicare Program Plans Holding Payments End of September 2006

The Centers for Medicare and Medicaid Services (CMS) announced plans to hold Medicare payments for 9 days on ALL claims (initial claims, adjusted claims, and Medicare Secondary Payer claims) that would be scheduled for payment September 22 through September 30, the end of its fiscal year. Payments that would have been paid during that period will be made on October 2, 2006, the first business day of the CMS new fiscal year. CMS currently has a mandatory 14-day hold on payments for electronic claims (29 days for paper claims), so in actual practice, you should expect to not see any Medicare checks from September 8 until October 2 for electronic claims. No interest will be paid on these delayed payments. The Deficit Reduction Act provided for this delay.

For more information, visit:
www.cms.hhs.gov/MLN MattersArticles/downloads/MM5047.pdf.

Medicare Physician Fee Schedule Proposed Rule

The Centers for Medicare and Medicaid Services (CMS) published a proposed rule in the *Federal Register* on June 29 that implements changes to the Medicare Physician Fee Schedule (MPFS). This rule results from CMS' congressionally mandated third Five-Year Review of physician work relative value units (RVUs). Work RVUs account for approximately \$35 billion in MPFS payments, representing more than 50% of overall Medicare payments under the fee schedule. Substantial increases are proposed for the physician work component of the Evaluation and Management Services and reflect the approved changes submitted to CMS by the Relative Value Update Committee (RUC) of the American Medical Association. ACCP actively participates in the RUC process. The physician work RVU changes are effective January 1, 2007.

► **Practice Expense:** Practice expenses account for approximately \$30 billion in MPFS payments, which represents

about 45% of overall MPFS payments. The practice expense changes propose a change in calculating the practice expense methodology to the "bottom-up" approach for calculating direct costs. This methodology change formalizes the work ACCP has been doing through the AMA RUC's Practice Expense Review Committee (PERC).

► **Impacts:** This proposed rule represents a shift of \$4 billion dollars for procedure and service specific payments within the Medicare physician fee schedule. The cognitive or nonsurgical specialties, including pulmonary medicine, would see increases of 5 to 7%. Critical care has a projected increase of 4%. Thoracic surgery has proposed increases of 1 to 2%. These increases relate to the specialty in aggregate. For the individual physician, payment would depend on the mix of services provided. Some surgical specialties would see cuts of 4 to 6%.

► **Great Success on Critical Care Codes:** We had a phenomenal success

on the critical care codes, 99291 and 99292, surveyed as part of the Five-Year Review. The total work component of the first hour of critical care up to 74 minutes, CPT 99291, in the facility setting (eg, hospital inpatient) is proposed to increase by 8.6%, and for each additional half hour, CPT 99292, a projected increase of 8.3% in the total RVU.

► **Results of Other Five-Year Reviewed Codes Surveyed:** There are modest increases to spirometry (CPT 94010) and subsequent ventilation management (94657), two other codes surveyed as part of the Five-Year Review. The subsequent ventilation management code was referred to the CPT Editorial Panel for revision to differentiate the work between the acute hospital inpatient/observation patient vs the long-term ventilated patient in a nursing facility setting.

► **Evaluation and Management Code Increases:** The good news is that the RUC valued changes to the

Continued on following page

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- Free 2-5 business-day ground shipping on orders over \$50.



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- Substantial discounts on software.
- Discounted 3-5 business-day ground shipping.
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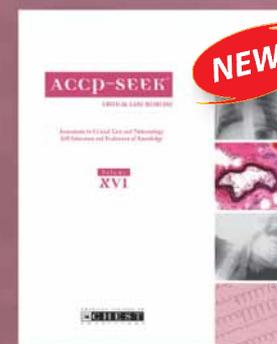
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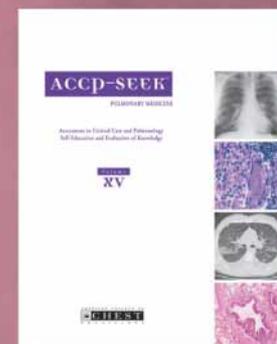
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NEWS FROM THE COLLEGE



Continued from previous page

Evaluation and Management Services were accepted in total by CMS. For example, the work component of the intermediate office visit for an established patient, CPT 99213, the most commonly billed physician's service, is projected to increase by 37%.

► **Budget Neutrality Work Adjuster:** The bad news is that due to congressionally mandated budget neutrality, CMS is proposing a 10% budget neutrality adjustment to the work RVUs that would only impact those services that have physician work RVUs. ACCP's comments to CMS strongly support that the budget neutrality adjuster be applied to

the conversion factor rather than the physician work component of the Medicare Physician Fee Schedule. CMS estimates that if applied to the conversion factor, the adjustment would be a -5%. For example, CPT 99213's national payment would be \$59.76. It would be \$59.50 if the 10% reduction was applied to the physician work component only. The results of CMS review of comments to this proposed rule will be published in their final rule in early November 2006.

If you have any questions, contact either Diane Krier-Morrow at dkriermorr@aol.com or (847) 677-9464, or Marla Brichta at ACCP at mbrichta@chestnet.org or (847) 498-8364. ■

Practice Management CHEST 2006 Lineup

Two half-day postgraduate courses entitled:

- Physician Reimbursement Essentials.
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24 additional educational sessions, such as:

- Practice Growth and Governance
- Electronic Medical Records (EMRs)
- Medicare Audits and Insurance Claims Denial

Practice Management Roundtables:

Back by popular demand, these will take place on Tuesday, October 24, in the exhibit hall from 11:55 am until 12:50 pm.

Pick up your free box lunch, look for the **red tablecloths.**

One-on-One Practice Management Consultations:

New this year, physicians and/or their practice administrators will have the opportunity to meet individually with our coding and reimbursement specialist. This is not to sell any services but rather to discuss problematic practice management issues with our expert consultant. Consultations will be scheduled in increments of 15 minutes, by appointment only. Please call Marla Brichta at (847) 498-8364. ■

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CPAP Lowered Blood Pressure in Sleep Apnea

Based on these reductions, 'You would expect to see improvement in morbidity and mortality.'

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

SAN DIEGO — Two weeks of continuous positive airway pressure significantly reduced the blood pressure of hypertensive obstructive sleep apnea patients in a small randomized controlled trial presented in a poster at the International Conference of the American Thoracic Society.

The patients in the trial ranged from 25 to 65 years of age with a mean body mass index of 29.5 kg/m²-31.5 kg/m². The only statistically significant difference in baseline characteristics was that average systolic blood pressure was lower in placebo patients: 122.5 mm Hg vs. 135.1 mm Hg in the CPAP group and 132.5 mm Hg in the oxygen cohort.

Mean arterial pressure at baseline was 91.2 mm Hg in the placebo group, 94.9 mm Hg in patients treated with oxygen, and 98.1 mm Hg in the CPAP group.

Average diastolic blood pressure was 75.6 mm Hg, 76 mm Hg, and 79.6 mm Hg, respectively.

Dr. Daniel Norman reported that nighttime systolic, mean arterial, and diastolic blood pressure decreased by 6 mm Hg, 5 mm Hg, and 4 mm Hg, respectively, in 18 patients on continuous positive airway pressure (CPAP).

Daytime mean arterial pressure (MAP) and diastolic blood pressure each declined by 3 mm Hg as well.

Although the difference was not statistically significant, daytime systolic blood pressure also dropped by about 2 mm Hg.

"This kind of improvement in blood pressure is similar to what you would see with many hypertensive medications," Dr. Norman, a fellow in pulmonary and

critical care at the University of California, San Diego Medical Center, said at a press briefing.

Based on these reductions, he added, "You would expect to see improvement in morbidity and mortality."

In contrast, 24-hour ambulatory blood pressure monitoring revealed no significant improvements in the blood pressure of the 13 patients who were treated with supplemental oxygen or of 15 patients on placebo.

The investigators adapted the equipment taken home by patients, so that the assigned apparatus looked the same regardless of which therapeutic option was delivered.

Though patients given supplemental oxygen did have better oxygenation saturation, this did not appear to have an impact on blood pressure, according to Dr. Norman and his coinvestigators in the departments of medicine and psychiatry at the university.

They speculated that CPAP's ability to improve blood pressure may involve "mechanisms other than improvement of nocturnal oxyhemoglobin saturation."

After 2 weeks of therapy, both the CPAP and supplemental oxygen groups registered improvements in average nocturnal saturation of oxyhemoglobin (SpO₂) and average SpO₂ nadir.

These values had been similar in all three groups at baseline, the investigators said, but the final SpO₂ values for both CPAP and supplemental oxygen patients were higher than those recorded in patients on placebo.

The apnea/hypopnea index and the oxygen desaturation index scores fell in the groups treated with CPAP or supplemental oxygen, but the investigators reported that "the magnitude of change was smaller in the oxygen group and not enough to differentiate it from placebo."

Dr. Norman noted that obstructive sleep apnea is known to increase the risk of hypertension.

He also acknowledged that half of the sleep apnea patients offered CPAP find they cannot tolerate it. Instead, they seek

other therapies, such as supplemental oxygen.

The trial doesn't rule out supplemental oxygen, he said, "but it reaffirms that CPAP remains the gold standard of therapy." ■

Dr. Susan H. Harding, FCCP, comments: This small study reaffirms the work of Becker M.F., et al. (*Circulation* 2003;107:68) who randomized 32 patients with severe OSA to CPAP or sham CPAP for an average of 9 weeks.

Mean blood pressure, as well as diastolic and systolic blood pressures, all decreased by approximately 10 mm Hg with therapeutic CPAP.

This drop in mean blood pressure would be predicted to reduce coronary artery disease event risk by 37%.

In another study, Doherty L.S., et al. (*Chest* 2005;127:2076) reported that patients utilizing CPAP had fewer total cardiovascular events (18%) compared to CPAP-intolerant patients (31%) over an average follow-up period of 7.5 years in 168 patients. CPAP can impact cardiovascular outcomes.

Auto-CPAP Appeared to Improve Adherence In Obstructive Sleep Apnea Patients

BY SHARON WORCESTER
Elsevier Global Medical News

SALT LAKE CITY — Automatically titrated continuous positive airway pressure appears to be an effective option for the management of obstructive sleep apnea in patients who fail to adhere to the standard of manually titrated CPAP.

Of 57 patients who were poorly compliant (defined in this study as using CPAP for 2-4 hours during a study night) or noncompliant (defined as using CPAP

for less than 2 hours during a study night), 72% were compliant with auto-CPAP, Vincenzo E. Castronovo, Ph.D., reported at the annual meeting of the Associated Professional Sleep Societies.

The patients were a subgroup of 509 consecutive patients with severe obstructive sleep apnea who underwent one full night of polysomnography with manual CPAP titration, and who were noncompliant during that night.

These patients received the auto-CPAP treatment one night after receiving the

manual titration CPAP, and used it for a mean of 6.7 hours with an average pressure of 8.4 cm H₂O and a 90th centile pressure of 10.2 cm H₂O, said Dr. Castronovo of the University Vita-Salute San Raffaele, Milan.

Compliance was defined in this study as CPAP use of more than 4 hours per night.

The findings suggest that auto-CPAP could be a valid therapeutic alternative in those patients who have poor compliance or who are deemed untreatable with CPAP.

Auto-CPAP should be considered before other treatment options, such as surgery, in these patients, Dr. Castronovo said. ■

Dr. Susan H. Harding, FCCP, comments: Because oral appliance therapy and uvulopalatopharyngoplasty have low success rates in patients with severe OSA, a concerted effort must be made to encourage the acceptance of positive airway pressure therapy by these patients. Desensitization therapy for claustrophobia, auto-CPAP, and even bilevel positive pressure should be considered for these patients.

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Computer Aids Stapling in Lung Resections

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO — A new computer-assisted stapling device is a significant advance over hand-operated staplers for minimal-access, muscle-sparing thoracotomy for anatomical lung resection, according to a presentation by Dr. Wickii T. Vigneswaran, FCCP.

The experience of two surgeons in their first 100 consecutive cases of using the SurgASSIST computer-assisted stapler suggests that it is safe and can be used effectively in minithoracotomy approaches for lung resection, Dr. Vigneswaran said at the annual meeting of the International Society for Minimally Invasive Cardiothoracic Surgery.

He and a colleague used the device in 84 lobectomies, five bilobectomies, five segmental resections, and six pneumonectomies performed in 56 men and 44 women.

The surgeries discussed included nine



The stapler has a microprocessor that measures tissue thickness and adjusts the pressure.
DR. VIGNESWARAN

complex resections, two sleeve lobectomies, six chest wall resections, and an extrapleural pneumonectomy. They fired a total of 502 staples (102 vascular, 91 bronchial, and 309 linear cutters) during the lung resections.

Compared with a hand-actuated stapler, the device had several advantages, reported Dr.

Vigneswaran, professor of surgery at the University of Chicago, and his associate in the study, Dr. Charles Gruner of Loyola University Medical Center, Maywood, Ill.

The computer-assisted stapler has a microprocessor that measures tissue thickness and adjusts the compression pressure, which isn't possible with hand-operated staplers.

The stapler's digital loading unit can be held by an assistant and the firing mechanism activated by the assistant or a nurse, leaving the surgeon's hands free to adjust the tissues and the placement of the loading unit.

The device has cables for right-angle, vascular, and bronchial stapling. Hand-operated staplers cannot do right-angled stapling, according to Dr. Vigneswaran.

The computer-assisted stapler can be used with a flexible shaft or a rigid extender.

"I find it difficult to control the flexible shaft," said Dr. Vigneswaran, who added that he prefers the rigid extender most of the time.

"Most of the operations are done from outside the chest cavity" in a muscle-sparing thoracotomy utilizing a 7- to 9-cm incision, "so it's very difficult to get your hands in," Dr. Vigneswaran noted.

Some technical problem were seen during the first 20 cases, including

incomplete sealing of a vein in one patient, early bronchial dehiscence in two patients, and one incident during their early experience with the flexible shaft in which the stapler failed to open automatically after closing.

In addition, the device "misread" the settings in 15% of patients, including communication errors between the computer and the digital loading device in 9% of patients.

The communication errors did not affect safety, he said.

The median operating time was 136 minutes. The duration of chest tube drainage lasted a median of 3 days, and patients spent a median of 5 days in the hospital.

One patient died from sepsis following aspiration pneumonia. Other complications in 20% of patients included prolonged air leaks in 8%, atrial fibrillation in 5%, and reoperations in 2% (1% for stump dehiscence resulting from inappropriate staple use and 1% for space problems).

Complications affecting 1% of patients each included hemothorax, chylothorax, *Clostridium difficile* colitis, myocardial ischemia requiring revascularization, and incarcerated ventral hernia.

The next generation of the device will feature some smaller components than did the first-generation version, Dr. Vigneswaran said.

Dr. Vigneswaran has received honoraria from the company that makes the computer-assisted stapling device, Power Medical Interventions Inc.



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 **DOSE 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. **Usage 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 DOSE 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 recommend-

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

ed 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

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

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

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

*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 DOSE AND ADMINISTRATION** sections of the complete prescribing information.)

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