

# CHEST *Physician*

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



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Following five procedures during central catheter placement improved Michigan ICU outcomes, said Dr. Peter Pronovost.

## Intervention Cut Central Catheter Infections by 66%

BY MARY ANN MOON  
*Elsevier Global Medical News*

A “simple and inexpensive” intervention to reduce ICU infections related to central catheter lines decreased the infection rate by 66% in 107 hospitals throughout Michigan, according to a new study.

The overall median rate of central catheter-related bloodstream infections per 1,000 catheter-days was held to zero throughout 18 months of follow-up, reported Dr. Peter Pronovost of Johns Hopkins University, Baltimore, and his associates.

“Important reductions in morbidity and health care costs could be achieved if the intervention ... could be introduced successfully nationwide or worldwide.

Given the results of the study, many of the estimated 80,000 infections, up to 28,000 deaths, and \$2.3 billion in costs attributed to these infections annually in the United States could be reduced,” the researchers said (*N. Engl. J. Med.* 2006;355:2725-32).

The intervention, part of a statewide program to improve patient safety, targeted clinicians’ use of five procedures identified by the Centers for Disease Control and Prevention as having the greatest potential to reduce infection and the greatest ease of implementation. The procedures are: appropriate hand washing, using full-barrier precautions during the insertion of central venous catheters, cleaning the

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## FDA Panel Votes To Strip Ketek of Two Indications

*Chronic bronchitis exacerbations nixed.*

BY ALICIA AULT  
*Elsevier Global Medical News*

SILVER SPRING, MD. — The antibiotic Ketek (telithromycin) is neither safe nor effective for treating acute exacerbation of chronic bronchitis or acute sinusitis, according to a Food and Drug Administration advisory committee that recommended that the agency remove those indications from the drug’s approved labeling.

The panel—a joint meeting of the FDA’s Anti-Infective Drugs and Drug Safety and Risk Management Advisory committees—concluded that although Ketek has been marketed since 2004, safety concerns argue against using the drug in two conditions that generally resolve on their own.

The panel voted 16-3 that Ketek should retain its approval for treating mild to moderate community-acquired pneumonia, but as a second- or third-line therapy. Ketek’s maker, Sanofi-Aventis, also presented

data suggesting that the drug may be effective against multidrug resistant *Streptococcus pneumoniae*, which was persuasive to the committee.

Although the panel supported keeping Ketek on the market, a majority of panelists recommended that a black box warning be added to the labeling.

“This is a drug that we need, but this is not something I’d reach for, and this is something I’d discourage people from using,” said Dr. Margo Smith, a panelist from the Washington Hospital Center.

If the FDA follows the panel’s advice, as it normally does, the agency would determine how to educate physicians on the revised uses. Sanofi-Aventis agreed that it would create a medication guide for consumers. FDA and Sanofi-Aventis would work out the content of the black box warning, which is likely to touch on the potential for liver toxicity, visual disturbances, loss of

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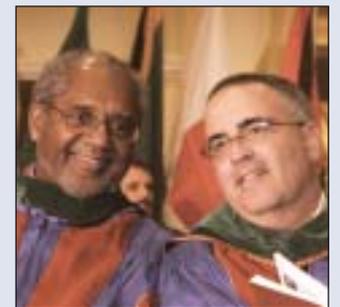
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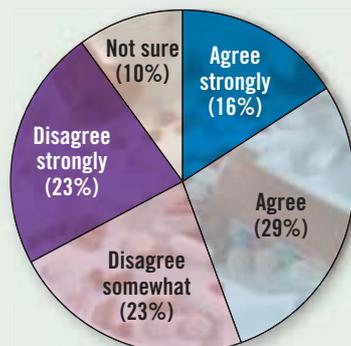
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#### Split Decision on Off-Label Drug Use

Doctors should be allowed to prescribe drugs to treat diseases or conditions other than those for which the drugs have been approved.



Notes: Online survey within the United States conducted Nov. 15-17, 2006, among a national cross-section of 3,018 adults. Percentages do not total 100 because of rounding. Source: Wall Street Journal/Harris Interactive

## Study: Ambrisentan Effective in PAH

BY BRUCE JANCIN  
*Elsevier Global Medical News*

SALT LAKE CITY — The investigational endothelin receptor antagonist ambrisentan appears to provide a more favorable risk/benefit ratio than current therapies do for pulmonary arterial hypertension, Dr. Lewis J. Rubin, FCCP, said at the annual meeting of the American College of Chest Physicians.

Results of the phase III randomized double-blind ARIES-I trial demonstrate that ambrisentan has good efficacy as once-daily oral therapy. What sets it apart from other effective endothelin receptor antagonists is that it displayed no liver toxicity in ARIES-I. No subjects developed liver function test abnormalities over

12 weeks, noted Dr. Rubin, professor of medicine at the University of California, San Diego.

Ambrisentan’s manufacturer, Gilead Sciences, last month submitted the drug for approval by the Food and Drug Administration for once-daily treatment of pulmonary arterial hypertension.

Ambrisentan is a high-affinity propanoic acid-class endothelin

receptor type A-selective agent with no interactions with warfarin or sildenafil.

Two oral twice-daily sulfonamide-class agents, bosentan (the endothelin receptor antagonist now on the market) and sitaxsentan (now under FDA review), are both associated with dose-dependent increases

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## Panel Debates Ketek Safety

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consciousness, and exacerbations of myasthenia gravis.

Ketek was under scrutiny during most of 2006. Senator Chuck Grassley (R-Iowa) has alleged that the drug was approved on the basis of a fraudulent trial, known as study 3014. On the eve of the 2-day FDA panel meeting, Sen. Grassley released results—so far—of his Finance Committee's investigation into the Ketek approval. He alleged that FDA managers failed to notify the Anti-Infective Drugs Advisory Committee when it met in 2003 that the agency had concerns about study 3014's integrity.

The panel recommended approval at that time, based in part on study 3014. The agency later held a closed-door meeting with the panel to discuss problems with study 3014, but Sen. Grassley alleges that the committee members still were not given a complete story.

In making the original approval decision, the agency determined that it could toss out tainted data from study 3014 and instead rely on postmarketing data collected on about 4 million patient exposures in Europe, said Dr. Janice Soreth, director of the FDA's division of anti-infective and

ophthalmology products, at the December meeting.

Several speakers at the FDA meeting—including a reviewer recently departed from the Ketek team—expressed outrage over the agency's reliance on postmarketing data instead of a prospective safety study for approval.

But the advisory panel did not seem as concerned.

The older postmarketing safety information—combined with updated surveillance reports from Europe and postmarketing data collected in the United States since Ketek's introduction—was presented at length.

FDA staffers disagreed on the incidence and import of side effects, as did the FDA and Sanofi-Aventis. Sanofi estimated that to date, the reporting rate in Europe for serious hepatic reactions is 4-10 cases/million courses of therapy. According to the FDA, from 2004 to 2006 there were 12 cases of acute liver failure among 5 million U.S. prescriptions, for a reporting rate of 23/10 million prescriptions. By comparison, the antibiotic Trovan (trovafloxacin) had a rate of 58 per 10 million in its first year on the market. The drug was subsequently recalled.

The FDA asked several experts from the Drug-Induced Liver Injury Network to take a closer look at 53 reports of hepatic toxicity associated with Ketek use. The network is a cooperative funded by the National Institute of Diabetes, Digestive, and Kidney Disorders.

One of those experts, Dr. William Lee, director of the clinical center for liver diseases at the University of Texas at Dallas, said that of the 53 patients, 44 were hospitalized, and there were five deaths and two liver transplants. The cases had similar clinical features, including rapid onset, prominent fever, joint aches, and right upper quadrant pain.

Dr. Lee said he believed that 28 of the 53 were very likely or probably caused by

Ketek, 17 were possibly related, and 8 had insufficient data to make a ruling. He said the hospitalization rate was probably 1 in 20,000 or 1 in 30,000 for liver toxicity and 1 in 150,000 for acute liver failure. Ketek's profile would be worse if it were a chronic medication, he said. "The severity may be limited simply because the drug exposure is quite short," Dr. Lee said.

Sanofi maintained that the hepatotoxicity was similar to that of other antibiotics. The panel was split on whether Ketek was an outlier.

Committee members were more concerned about exacerbations of myasthenia gravis, a neurological condition affecting 35,000-70,000 Americans. But many individuals aren't aware they have the condition and might unwittingly take Ketek. The drug's label already includes a warning against use in affected patients, but that has not stopped such use.

The FDA's review found 33 reports of exacerbations of myasthenia gravis since 2004. Of those, seven were life threatening and 12 patients required a ventilator or intubation.

There were 71 cases of vision disorders and 23 cases of disturbances in consciousness with serious outcomes. In one case, an 18-year-old passed out while driving and struck and killed a pedestrian.

Sanofi-Aventis stuck to its data showing that Ketek was no different from other drugs in the class. "Overall, we believe that the safety risks with telithromycin appear to be similar to widely prescribed antibiotics," said Dr. Bruno Leroy, head of the company's internal medicine franchise.

Some FDA staffers were not convinced. "Ketek stands out among the macrolides in its unique and notable toxicity," said Dr. Rosemary Johann-Liang, deputy director of the division of drug risk evaluation at FDA's Center for Drug Evaluation and Research.

Ketek has been prescribed to 6 million U.S. patients since 2004, according to Sanofi-Aventis. "Sanofi-Aventis will be in further discussion with the FDA regarding today's recommendations," the company said in a statement after the meeting. ■

## Five Steps

Central Catheter • from page 1

with chlorhexidine, avoiding the femoral site for access if possible (i.e., using the subclavian vein when possible), and removing unnecessary catheters.

A hospital-based practitioner was designated as the infection-control specialist. Clinicians were taught infection-control practices, provided with a central-line cart with necessary supplies, given a checklist to ensure adherence to infection-control practices, and stopped if they weren't following the checklist. Catheter removal was discussed every day at rounds, and ICU teams received feedback on infection rates at monthly and quarterly meetings.

This intervention was assessed at 67 Michigan hospitals of all types, including 103 medical, surgical, cardiac, neurologic, and trauma ICUs and 1 pediatric ICU.

Within 3 months of implementation, the overall median rate of central catheter-related bloodstream infection dropped from 2.7 per 1,000 catheter-days at baseline to 0. The corresponding average rates of infection were 7.7 and 2.3, respectively, Dr. Pronovost and his associates said.

This 66% decline was sustained throughout 15 more months of follow-up. It was seen in both teaching and nonteaching hospitals, and in both small and large hospitals.

These results show that large-scale implementation of such a program is feasible and effective, the investigators added.

In an editorial comment accompanying this report, Dr. Richard P. Wenzel and Dr. Michael B. Edmond of Virginia Commonwealth University, Richmond, termed the real-world efficiency of the intervention "extraordinary."

The intervention's results were "compelling, and the costs and efforts so relatively minor that the five components of the intervention should be widely adopted," they said (N. Engl. J. Med. 2006;355:2781-3). "Imagine the effect if all 6,000 acute care hospitals in the United States were to show a similar commitment and discipline." ■

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# Think of COPD as a Multisystem Disease

*COPD takes its heaviest extrapulmonary toll on the cardiovascular, muscular, and skeletal systems.*

BY BRUCE JANCIN  
Elsevier Global Medical News

SALT LAKE CITY — It's high time to recognize that chronic obstructive pulmonary disease is a multisystem disorder extending well beyond the lungs, Dr. Stanley B. Fiel, FCCP, said at a satellite symposium held in conjunction with the annual meeting of the American College of Chest Physicians.

Chronic obstructive pulmonary disease (COPD) is best viewed as a systemic inflammatory disorder, not merely an inflammatory disorder of the respiratory tract. The extrapulmonary systems where COPD takes its heaviest toll are the cardiovascular, muscular, and skeletal.

Even among patients with severe COPD, only about one-quarter of deaths are due to COPD. Among those with moderate COPD, it's closer to 5%. The predominant cause of mortality in COPD patients is atherosclerotic cardiovascular disease, added Dr. Fiel, chairman of medicine at Morristown (N.J.) Memorial Hospital. He has served as a consultant to Altana Pharma, which sponsored the satellite symposium.

## Cardiovascular Risk

Major contributions to understanding the association between COPD and cardiovascular risk have been provided by Dr. Don D. Sin, FCCP, of the University of British Columbia, Vancouver, and his coinvestigators. They showed in an analysis of 1,861 participants in the first National Health and Nutrition Examination Survey Epidemiologic Followup Study that a reduced forced expiratory volume in 1 second (FEV<sub>1</sub>) is a risk factor for cardiovascular hospitalization or mortality independent of smoking history, Framingham risk score, and other potential confounders. Individuals in the lowest FEV<sub>1</sub> quintile had a 5.6-fold increased risk of fatal ischemic heart disease, compared with those in the top quintile. That was true even across a relatively narrow range of FEV<sub>1</sub> declines, from a mean of 109% to 88% of predicted (Chest 2005;127:1952-9).

As part of the same report, the Canadian investigators conducted a meta-analysis of 12 large published cohort studies that looked at cardiovascular mortality based on FEV<sub>1</sub> in nearly 84,000 subjects.

Those in the worst FEV<sub>1</sub> quintile had an adjusted 75% increased risk of cardiovascular mortality, compared with those in the best quintile.

"So why don't primary care physicians do more routine measuring of FEV<sub>1</sub>? It's a good question, since we know that just as blood pressure is an independent risk factor for cardiovascular mortality, so is FEV<sub>1</sub> in patients regardless of whether they smoke or don't smoke," Dr. Fiel said.

One major difference between high blood pressure and low FEV<sub>1</sub> as cardiovascular risk factors, however, is that as yet there are no prospective data demonstrating how to intervene effectively in COPD patients to reduce their cardiovascular risk, he conceded. Investigative interest in potential targets for preventive therapy is focused on the elevated levels of fibrinogen, neutrophils, platelets, and C-reactive protein that Dr. Sin and his coworkers documented in patients with stage 3 and 4 COPD (Circulation 2003;107:1514-9).

## Bone Abnormalities

British investigators have reported a dual-energy x-ray absorptiometry study showing that osteoporosis or osteopenia was present in fully 89% of a group of COPD

patients with an FEV<sub>1</sub> less than 50% of predicted, corresponding to Gold stage 3 or 4 disease. Among patients with COPD and an FEV<sub>1</sub> greater than 50% of predicted, osteoporosis or osteopenia was present in 69% (Am. J. Respir. Crit. Care Med. 2004;170:1286-93).

Other studies have shown that the bone density abnormalities in COPD can't simply be explained away as being a consequence of prolonged use of corticosteroids. Such abnormalities are present in most steroid-naïve patients with advanced COPD.

## Skeletal Muscle Atrophy

Loss of fat-free mass in patients with COPD is common and is associated with reduced endurance, poor quality of life, and decreased exercise ability. Dutch investigators recently reported that the prevalence of abnormal body composition—a low body mass index and/or low fat-free mass index—was 43% among women and 21% in men in a cohort of 389 outpatients with moderate to severe COPD (Respir. Med. 2006;100:1349-55).

The intermediary between systemic inflammation and cachexia in COPD is thought to be the nuclear transcription factor kappa beta, Dr. Fiel said. ■

## When Defining COPD in the Elderly, It May Be Best to Go With the GOLD

BY BRUCE JANCIN  
Elsevier Global Medical News

SALT LAKE CITY — The use of an age-adjusted lower limit of normal in the FEV<sub>1</sub>/FVC ratio to define chronic obstructive pulmonary disease in the elderly results in a large problem of underdiagnosis, Dr. David M. Mannino, FCCP, said at the annual meeting of the American College of Chest Physicians.

The Global Initiative on Obstructive Lung Disease (GOLD) criteria provide a better approach to defining abnormal lung function in the elderly. The GOLD standard relies on a fixed ratio of the postbronchodilator



**The group whose FEV<sub>1</sub>/FVC was less than 0.70 but above the LLN had a 30% increased risk of mortality.**

DR. MANNINO

declines with age. For example, the ratio's lower limit of normal (LLN) slips below 0.70 at age 52 years in white women, 41 years in white men, 54 years in black women, and 48 years in black men. Reliance on the GOLD criteria might result in overdiagnosis of mild COPD in the elderly.

In response to this argument, the latest American Thoracic Society/European Respiratory Society guidelines for interpreting spirometry, published in 2005, recommend adopting the age-adjusted LLN to classify obstruction on spirometry. But this has a problem: It is based on analysis of cross-sectional data. And cross-sectional data do not

provide any information about longitudinal outcomes—which is what really matters, Dr. Mannino said.

To elevate the debate by introducing outcomes data, he and his coinvestigators turned to the National Institutes of Health-sponsored prospective epidemiologic Cardiovascular Health Study. He reported on 4,965 study participants aged 65 years and older who underwent baseline spirometry and up to 11 years of follow-up. Twelve percent were current smokers, and

42% were former smokers; 95% were white, and 57% were women. The population of interest in this analysis was the 1,134 subjects whose baseline FEV<sub>1</sub>/FVC was less than 0.70 but above the LLN.

Death occurred in 32.6% of the 4,965 subjects during follow-up, and 18.8% had one or more COPD-related hospitalizations. The subgroup whose FEV<sub>1</sub>/FVC fell between 0.70 and the LLN had an adjusted highly significant 30% increased risk of mortality and a 2.6-fold risk of COPD-related hospitalization during follow-up, compared with asymptomatic subjects with normal lung function.

"If these people were characterized using the LLN, they would all be counted as normal—and they're clearly not normal," Dr. Mannino noted, adding that intervention would likely help these patients. ■

## Dr. Mark Dransfield comments:

*Although we all lose lung function with age, it is difficult to characterize this process as truly normal. Dr. Mannino clearly has shown that patients with airflow limitation, as defined by GOLD criteria, are at increased risk for death and COPD morbidity, even when their FEV<sub>1</sub>/FVC ratio is above the LLN. A parallel can be drawn with presbycusis. Although age-related hearing loss is common, it cannot be viewed as normal, and being deaf feels the same whether you are 40 or 75.*

## Ask Blue-Collar Patients About Smoking

WASHINGTON — Significantly fewer white-collar workers than blue-collar workers are smokers, according to National Health Interview Survey data from more than 140,000 respondents.

Pooled smoking data from 1997 to 2004 showed the highest reported rates among construction workers (39%) and the lowest reported rates among health professionals (5%), said David J. Lee, Ph.D., who presented the findings at a conference on tobacco control sponsored by the American Cancer Society.

"The overarching goal of Healthy People 2010 is to reduce health disparities in the U.S. population, and I think you'll agree that we have a health disparity here with respect to smoking groups," said Dr. Lee of the epidemiology and public health department at the University of Miami.

Dr. Lee cited his study of 8-year smoking trends by occupational category based on NHIS data in which the 20 occupations with the highest smoking rates (all greater than 40%) were blue-collar jobs, and included bartenders, waiters, maintenance workers, truck

drivers, and carpenters (J. Occup. Environ. Med. 2004;46:538-48).

"We saw some evidence of a smoking decline [among] roofers (who topped the list with a 58% smoking rate), but it was not statistically significant," he said.

By contrast, the occupations with the 20 lowest smoking rates were classified as white-collar jobs, and ranged from 15% among airline pilots to 4% among clergy and physicians.

Despite evidence of declining smoking rates in some blue-collar professions, the findings suggest that blue-collar workers need more attention from their employers and health professionals if they are going to stop smoking.

Workplace health and safety programs offer excellent opportunities to encourage smokers to quit, especially those who rarely see a physician in the office, Dr. Lee said. But office-based physicians who ask their blue-collar patients about smoking and assist those who want to quit are essential to reducing the occupational disparity, he emphasized.

—Heidi Splette

# Studies Support Safety of Long-Acting $\beta$ -Agonists

BY BRUCE JANCIN  
Elsevier Global Medical News

SALT LAKE CITY — Reassurance about the cardiovascular safety of long-acting  $\beta_2$ -agonists in patients with chronic obstructive pulmonary disease was provided by two large studies presented at the annual meeting of the American College of Chest Physicians.

Sarika S. Ogale presented a nested case-control study involving 104,459 predominantly elderly male patients with newly diagnosed COPD in the national Department of Veterans Affairs database. During an average follow-up of 1.5 years and a maximum of 5.8 years, 6,954 of the patients were hospitalized for acute coronary syndrome, heart failure, or cardiac arrhythmia. Heart failure was the primary admitting diagnosis in nearly 3,100 patients, with the remainder being split roughly equally between ACS and arrhythmia. The control group consisted of 34,770 VA patients matched for age and duration of COPD.

After adjusting for COPD severity as reflected in the number of exacerbations in the year prior to the event, use of other medications, cardiovascular risk factor profiles, and other factors, the cardiovascular event rate in COPD patients who had ever used long-acting  $\beta$ -agonists (LABAs) proved to be virtually identical to that in never users, according to Ms. Ogale, a graduate student in the pharmaceutical outcomes research program at the University of Washington, Seattle.

She and her coworkers also broke down the data by comparing cardiovascular event rates in patients who had used

LABAs for 0-4 months with those in patients who had a greater than 4-month history of cumulative exposure to LABAs. They chose 4 months as the cutoff because that was the median duration of usage in the study. Once again, event rates were virtually identical in the group with less or no LABA exposure and the group with longer duration of LABA usage.

The investigators next plan to reanalyze the data looking at all-cause mortality. They also want to see if the results vary by racial group.



Event rates were identical in the group with less or no LABA exposure and the group with longer usage.

MS. OGALE

Short-acting  $\beta$ -agonists such as albuterol have been associated with an increased risk of cardiovascular events in observational studies. LABAs were linked to increased mortality in African American asthmatics in the Salmeterol Multicenter Asthma Research Trial (SMART), whose findings have come under heavy criticism. But the cardiovascular safety of LABAs in the COPD population has previously been looked at mainly in studies too short in duration to be conclusive.

In a separate presentation, Dr. Bartolomeo R. Celli, FCCP, said there was no hint of increased mortality in the salmeterol arm of the landmark Towards a Revolution in COPD Health (TORCH) study.

In fact, there was a nonsignificant trend for greater survival in the salmeterol arm than in the fluticasone arm of the 3-year double-blind trial in which 6,112 COPD patients were randomized to twice-daily salmeterol, fluticasone, placebo, or the salmeterol/fluticasone combination known in the United States as Advair and in Europe as Seretide, according to Dr. Celli, professor of medicine at Tufts University, Boston.

# Resistance Can Torpedo CAP Treatment With Macrolides

Failures often occur at MICs less than 16 mcg/mL.

BY SHERRY BOSCHERT  
Elsevier Global Medical News

SAN FRANCISCO — Drug resistance was a common cause of treatment failure in 26 patients with community-acquired pneumonia who developed bacteremia while being treated with macrolide antibiotics, Dr. Gavin Bayan Grant said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Of the 26 patients who developed bacteremia while on erythromycin, clarithromycin, or azithromycin therapy, 21 (81%) had resistant organisms, compared with 15 (44%) of 34 patients who developed bacteremia after recent use of one of the macrolides (defined as 16-90 days before the bacteremia diagnosis) and 14% of 721 patients who had not been taking any antibiotics and developed bacteremia.

Macrolide antibiotics are standard therapy for outpatient treatment of pneumonia, and evidence that significant macrolide resistance occurs has been inconclusive, said Dr. Grant of the Centers for Disease Control and Prevention, Atlanta.

The current findings provide further evidence that resistance can lead to treatment failure with macrolides, which may inform clinical decisions to change antibiotics in some patients, he said at the meeting, sponsored by the American Society for Microbiology.

Dr. Grant has no association with the companies that make macrolides.

After controlling for patient age, immunosuppression, chronic comorbidities, and residence in a long-term care facility, patients failing macrolide therapy were 5 times more likely to have

resistant organisms, compared with patients who developed bacteremia after recent macrolide use, and 26 times more likely to have resistance than patients with bacteremia who had not been taking antibiotics.

The study also found that clinicians who define macrolide resistance using a cutoff of a minimum inhibitory concentration (MIC) of at least 16 mcg/mL will miss a significant percentage of the treatment failures.

"Failures often occur at macrolide MICs less than 16 mcg/mL," Dr. Grant said.

The laboratory-defined cutoff for pneumococcal resistance to erythromycin is 1 mcg/mL. Some researchers, however, have advocated the 16 mcg/mL cutoff value as more likely to result in breakthrough bacteremia, Dr. Grant explained.

Comparison of isolates from all three patient groups found that breakthrough bacteremia occurred at a broad range of MIC values above 1 mcg/mL, not just at the higher levels of resistance, Dr. Grant said.

Among patients with MIC values of 1 mcg/mL or greater, the distribution of MICs did not differ significantly between groups.

An MIC of 16 mcg/mL or greater was observed in 39% of the group who failed macrolide therapy and in 6% of patients who developed bacteremia after recent macrolide therapy or not taking antibiotics.

**Dr. Susan Harding, FCCP, comments:**

We need to recognize potential treatment failures because of macrolide resistance, especially in patients who have recently used macrolides.

# Drug's Liver Effects Limited

Ambrisentan • from page 1

in liver function abnormalities that can force treatment discontinuation.

The ARIES-I trial involved 202 patients with pulmonary arterial hypertension (PAH) who were randomized to 12 weeks of double-blind placebo or once-daily ambrisentan at 5 mg or 10 mg.

Roughly two-thirds of patients had idiopathic pulmonary arterial hypertension. Most others had pulmonary arterial hypertension associated with connective tissue disease.

Most subjects had moderate disease; 58% of patients were World Health Organization class III, while 32% of patients were class II.

The study patients' mean baseline 6-minute walk distance was

341 m, which is indicative of moderate impairment.

The primary study end point was change in 6-minute walk distance over 12 weeks. It increased by 43.6 m with 10 mg/day of ambrisentan and 22.8 m with 5 mg, and it decreased by 7.8 m on placebo, suggesting a possible dose-response effect.

ARIES-I broke new ground as the first trial in pulmonary arterial hypertension to use change in plasma brain natriuretic peptide (BNP) as a secondary end point.

BNP is a marker of right heart stress. It reflects severity of PAH and is predictive of long-term outcome.

BNP dropped by a mean of 62.5 and 149.3 pg/mL in patients on 5 and 10 mg/day

of ambrisentan, respectively, while climbing 11.8 pg/mL with placebo.

In terms of other secondary end points, the Borg dyspnea index showed significant improvement in ambrisentan-treated patients.

They were also only half as likely to experience clinical worsening during the study period.

The ambrisentan arms of the ARIES-1 trial showed nonsignificant trends toward improvement in World Health Organization functional class and on the Short Form-36 physical function scale.

Ambrisentan's chief side effects were peripheral edema, occurring in more than one-

quarter of patients, and nasal congestion, in 9%.

The edema is an endothelin receptor antagonist-class effect.



The incidence of liver function test abnormalities in the ARIES-I phase III trial was zero.  
DR. RUBIN

It is typically mild and readily managed with low-dose diuretics without need for dose adjustment of the anti-PAH drug, Dr. Rubin said.

During a mean extended follow-up of 1.4 years and a maximum of 2.8 years, the incidence of confirmed liver function test abnormalities in the ARIES-1 participants who were treated with ambrisentan was 0.5%.

That's less than the 3% incidence noted in the placebo arm during the 12-week double-blind treatment period.

Dr. Rubin is a consultant to

Myogen Inc., the company that sponsored the ARIES-I clinical trial.

Gilead Sciences acquired Myogen in November 2006, and will market ambrisentan in the United States. GlaxoSmithKline will market ambrisentan outside the United States.

**Dr. Thomas Behrenbeck, FCCP, comments:** Ambrisentan is a new representative of the endothelin receptor antagonist class, one of the three major mechanistic pathways known to be affected in patients with pulmonary arterial hypertension.

This study is encouraging, as the drug does not seem to cause liver function abnormalities, which have limited treatment with the other drugs of the class.

It still remains to be seen if ambrisentan will have a beneficial effect on the long-term outcome of these patients.

# Home Nebulizer Misuse Cited in Asthma Deaths

BY BRUCE JANCIN  
Elsevier Global Medical News

SALT LAKE CITY — Misuse of home nebulizers appears to be an important factor in many asthma deaths in children and young adults, Dr. Amit Gupta said at the annual meeting of the American College of Chest Physicians.

His retrospective study of all 86 asthma deaths in 2- to 34-year-olds in Michigan in 2002-2004 concluded that many involved individuals had a home nebulizer but weren't using it in accordance with the NIH-National Asthma Education and Prevention Program guidelines.

"The widespread prescription and use of home nebulizers in asthma may lead to an



Surprisingly, 35% of adult fatalities occurred in people with moderate persistent asthma.

DR. GUPTA

overreliance on bronchodilators and underuse of steroids. This may lead to subsequent delay in seeking medical care during an acute exacerbation, or to poor chronic control of asthma, which may eventually lead to a poor outcome," said Dr. Gupta of Michigan State University, East Lansing.

The study fo-

focused on 86 asthma deaths in Michigan; 48 of these deaths involved 19- to 34-year-olds. Of the 38 pediatric deaths, all but 1 occurred in children at least 5 years old.

A panel of experts reviewed medical records for 1 year before death as well as death certificate data and the results of next-of-kin interviews obtained in 61 cases.

Surprisingly, 35% of adult fatalities occurred in people with moderate persistent asthma, Dr. Gupta noted.

National Asthma Education and Prevention Program guidelines recommend limiting the use of home nebulizers to acute asthma exacerbations that are monitored with a peak flow meter (PFM). Patients whose symptoms and peak flow readings don't improve after a single use are supposed to seek immediate medical attention. And all patients prescribed a home nebulizer are supposed to have a written asthma action plan to guide them in the event of an acute exacerbation or emergency.

The Michigan investigators found that 52 patients had a home nebulizer, but only 9 had a written asthma action plan—and none used it to monitor their disease. Sixteen percent of children and more than 50% of adults with a nebulizer used it regularly, with frequencies ranging from once per week to six times daily.

Study findings revealed that 38 patients had a PFM, including 29 with a home nebulizer. More than half of children with a PFM used it regularly; none of the adults did. Nineteen individuals used their home nebulizer prior to their fatal asthma attack; only 9 of the 19 did so in conjunction with use of a PFM.

All 52 patients who had a home nebulizer met national guidelines criteria for the use of chronic corticosteroids as asthma

control medication, but inhaled or oral steroids were prescribed in only two-thirds of those patients. Moreover, only 11 of 52 were using steroids as prescribed, continued Dr. Gupta.

The next-of-kin interviews as well as patient behavior suggested home nebulizers had provided the deceased with a false sense of security during acute exacerbations. Moreover, the rapid symptomatic relief obtained with use of the nebulizer led many patients to use nebulized bronchodilators frequently, resulting in poor

chronic control of their respiratory disease—exactly the sort of vicious circle that the national guidelines were designed to prevent.

Asthma morbidity and mortality in the United States remain "unacceptably high," he said. An estimated 4,000 people die each year from asthma. The disease results in 7.5 million preventable sick days annually. In Michigan alone, there are roughly 30,000 hospitalizations for asthma each year.

He proposed several interventions to improve home nebulizer safety: dispensing

the devices only together with a PFM and a written asthma action plan; pharmacist notification to physicians regarding frequent bronchodilator refills; and better patient and physician education about home asthma management.

One pediatrician in the audience observed, "When home nebulizers are prescribed by ER docs and other physicians who don't appreciate enlightened asthma management, you plug the nebulizer in and you unplug the physician from the equation." ■

# IPF

## Help us explore the way we look at idiopathic pulmonary fibrosis (IPF)

IPF has been associated with increased levels of endothelin (ET), a 21-amino acid peptide with diverse biological functions and pathological effects.<sup>1</sup> Patients with IPF demonstrate elevated ET plasma concentrations and ET expression in the lung tissue,<sup>2</sup> and ET concentration has been found to correlate with disease activity.<sup>3</sup> Through ongoing research we are exploring the link between ET and the disease of IPF.

 ACTELION

# Ringer's May Be Safer Than Starch Solutions in Sepsis

BY MICHELE G. SULLIVAN  
Elsevier Global Medical News

BARCELONA — Hydroxyethyl starch solutions can't be recommended for fluid resuscitation in patients with severe sepsis or septic shock, or in those at risk of renal problems, researchers said at the annual congress of the European Society for Intensive Care Medicine.

The starch solutions are associated with higher rates of acute renal failure and increased 90-day mortality in these patients,

especially in those who receive more than the highest recommended dosage of 22 mL/kg of body weight, said Dr. Frank M. Brunkhorst of the Friedrich Schiller University of Jena (Germany).

Dr. Brunkhorst, who also manages the German Sepsis Society, reported the interim results of the Influence of Colloid vs. Crystalloid Volume Resuscitation in Patients with Severe Sepsis and Septic Shock (VISEP) study. VISEP, a phase III trial, randomized patients to volume replacement with either 10% hydroxyethyl starch

(HES) 200/0.5 solution (10% Hemohe) or Ringer's lactate solution.

The study was powered for 1,200 patients, but it was suspended after the first interim analysis of 600 showed trends of increased renal failure and mortality in the HES group, Dr. Brunkhorst said.

All patients in the study had either severe sepsis or septic shock; their mean age was 64 years. The mean Acute Physiology and Chronic Health Evaluation II score was 20, and the mean Simplified Acute Physiology Score (version II) was 53.

Hemodynamic stabilization occurred significantly faster in the HES group. Mortality at 28 days was slightly but not significantly higher in the HES group, compared with the Ringer's lactate group (27% vs. 24%), a trend repeated for 90-day mortality (41% HES vs. 34% Ringer's lactate).

There were no significant differences in the Sequential Organ Failure Assessment scores overall. However, the coagulation and renal subscores were significantly higher in the HES group, Dr. Brunkhorst said.

In addition, almost twice as many HES as Ringer's patients needed hemodialysis during their treatment (31% vs. 19%), with a total of 650 days of dialysis in the

**THE STARCH SOLUTIONS ARE ASSOCIATED WITH HIGHER RATES OF ACUTE RENAL FAILURE AND INCREASED 90-DAY MORTALITY.**

## A landmark IPF morbidity and mortality trial is under way

Patients are now enrolling in a new IPF trial called BUILD-3.

Inclusion criteria include age over 18 years, biopsy-proven IPF diagnosis, and disease duration less than 3 years. Exclusion criteria include interstitial lung disease due to conditions other than IPF, and severe restrictive lung disease.

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(Identifier # NCT00391443)

**BUILD** 

HES group and 321 days in the Ringer's group. Acute renal failure rates were also higher in the HES group (35% vs. 23%).

The highest recommended dosage of HES (22 mL/kg) was exceeded in 99 patients. A subanalysis of this group identified a dose-dependent mortality increase at 90 days: 75% of those who exceeded the dosage and 49% of those who did not died. "This was highly statistically significant," Dr. Brunkhorst said.

No previous study identified increased mortality with high HES doses, he said—probably because the observation period was too short. "All the other studies had a follow-up of only a few days. This was a phenomenon observed only after 3 weeks."

In 2003, when the VISEP study began, 10% HES was the lightest molecular weight and most rapidly degrading colloidal fluid replacement solution available, said Dr. Konrad Reinhart, a coinvestigator of the VISEP trial. Since then, lighter solutions have come to market. But he said that no studies have demonstrated enough treatment superiority to convince him to use any colloidal solution instead of Ringer's.

There are many case reports of pruritic dermatitis associated with starch deposits in the dermis. Autopsy reports have also shown starch deposits in kidney and liver that persisted for more than 10 years after HES treatment, said Dr. Reinhart, director of the department of anesthesiology and intensive care medicine at the University Hospital of the Friedrich Schiller University of Jena.

Dr. Reinhart is also not convinced that acute renal failure is the only factor involved in the increased risk of death in HES patients. "Several case reports have looked at foamy macrophage syndrome in these patients," he said (*Ann. Int. Med.* 2002;137:1013-4).

He said his institution has restricted the use of starch solutions. "We have stopped using them in our unit, and I won't use them at all in sepsis patients," Dr. Reinhart said. "No data have ever demonstrated a beneficial effect [over Ringer's], but a lot have demonstrated harm." ■

1. Fagan KA, McMurtry IF, Rodman DM. Role of endothelin-1 in lung disease. *Respir Res.* 2001;2:90-101. 2. Uguccioni M, Pulsatelli L, Grigolo B, et al. Endothelin-1 in idiopathic pulmonary fibrosis. *J Clin Pathol.* 1995;48:330-334. 3. Giaid A, Michel FP, Stewart DJ, Sheppard M, Corrin B, Hamid O. Expression of endothelin-1 in lungs of patients with cryptogenic fibrosing alveolitis. *Lancet.* 1993;341:1550-1554.

# Radiation Upped Survival in Lung Cancer With Metastasis

BY BRUCE WILSON  
Elsevier Global Medical News

PHILADELPHIA — Postoperative radiation therapy and chemotherapy for patients with non-small cell lung cancer that has spread to the mediastinal lymph nodes allowed them to survive twice as long as patients who do not receive radiation, according to a study presented at the annual meeting of the American Society for Therapeutic Radiology and Oncology.

In addition, a subanalysis of the ANITA (Adjuvant Navelbine International Trialists Association) 1 trial showed that in the absence of adjuvant chemotherapy, postoperative radiation therapy (PORT) improved 5-year survival in patients with nodal status N1 and N2, but was harmful for patients with N0 status (no regional lymph node metastasis). With adjuvant chemotherapy, PORT improved survival in N2 patients but was harmful to N1 and N0 patients.

The multinational ANITA 1 trial enrolled 840 patients with stage IB-IIIa non-small cell lung cancer and randomly assigned them to observation (433 patients) or a chemotherapy regimen of vinorelbine plus cisplatin (407 patients). All patients had been totally resected within 42 days before enrollment.

“Radiation was neither manda-

tory nor randomized but only recommended by protocol in patients with node-positive disease,” said lead author Dr. Jean-Yves Douillard, professor of medical oncology at René Gauducheau University of Nantes, France. A total of 232 patients with node-positive disease received PORT: 144 patients (33%) in the observation arm, and 88 (22%) in the chemotherapy arm.

In the intention-to-treat (ITT) analysis, patients who received chemotherapy survived a median of 65.7 months, compared with 43.7 months for the observation arm, a significant difference (Lancet Oncol. 2006;7:719-27).

Overall survival at 5 years with chemotherapy improved by 8.6%, an improvement that was maintained at 7 years (8.4%). When examined by stage, the authors found no difference in survival between the arms in stage I patients. However, stage II patients treated with chemotherapy had a nonsignificant 12.6% survival advantage at 5 years. A univariate analysis of the ITT population showed that all patients who received PORT had a distinct, significant survival advantage.

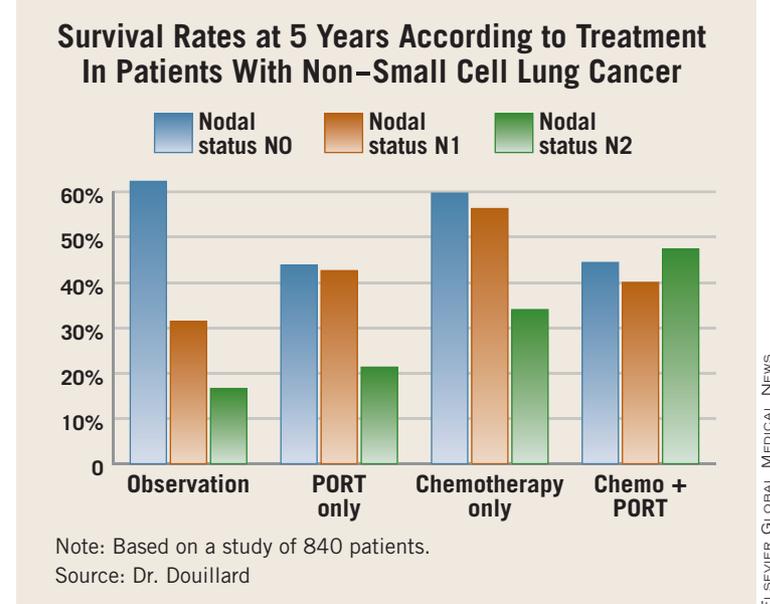
The subanalysis of patients who received PORT showed an overall 5-year survival of 51 months in the chemotherapy arm and 43 months in the observation arm. However,

when broken down by nodal status, patients with N1 disease who received chemotherapy plus PORT had lower median survival rates than those who received chemotherapy alone (46.4 months vs. 96.3 months, respectively). Conversely, N1 patients who received PORT alone did better than those who had no chemotherapy or PORT (50.2 months vs. 25.9 months).

On the other hand, patients with N2 disease received benefit with additional PORT, with or without chemotherapy. Patients who received chemotherapy plus PORT survived longer than those who received chemotherapy alone (47.4 months vs. 23.8 months, respectively), whereas those who received PORT alone survived longer than those who received no treatment (22.7 months vs. 12.7 months).

Dr. Douillard stressed that the results are a descriptive analysis and should be interpreted with caution. They will be tested in a randomized trial being planned.

These findings are in line with those of other studies in which radiation appears to be of benefit for patients with N2 disease, but not for patients with N1 or N0 disease, Dr. Benjamin Movsas wrote in an accompanying editorial (J. Clin. Oncol. 2006;24:2998-3006). “In this study, there was absolutely no increased risk for



patients with N2 disease, and it was the patients with the least to gain—N0 and N1 patients—who had the most to lose,” said Dr. Movsas, chairman of the department of radiology at the Henry Ford Health System, Detroit.

An important component of the ANITA 1 trial was the sequencing of PORT after adjuvant chemotherapy. An earlier trial demonstrated no survival advantage by combining chemotherapy and radiation therapy postoperatively (N. Engl. J. Med. 2000; 343:1217-22). Dr. Movsas said this suggests that physicians should start with chemotherapy to achieve an overall survival benefit,

followed by radiotherapy for local recurrence and disease-free survival benefits.

“This is the sequential strategy that was used in the ANITA trial for patients that received both chemotherapy and radiation,” he said. The results suggest that as systemic control and overall survival improve, the importance of local control increases.

Until the results of the randomized trial are in, Dr. Movsas recommended that patients with N2 disease be given the option of PORT after adjuvant chemotherapy, because the benefits in terms of local control and disease-free survival outweigh the risks. ■

## New Staging Technique Beat the Standard in NSCLC Trial

BY JANE SALODOF MACNEIL  
Elsevier Global Medical News

STOCKHOLM — Transcervical extended mediastinal lymphadenectomy, a new technique for staging non-small cell lung cancer patients, proved superior to standard cervical mediastinoscopy in a clinical trial presented at a meeting of the European Association for Cardio-Thoracic Surgery.

Dr. Jaroslaw Kuzdzal reported that transcervical extended mediastinal lymphadenectomy (TEMLA) found positive nodes in 7 of 21 patients. No mediastinal metastases were subsequently detected in 13 patients who underwent thoracotomy after TEMLA staged them as node negative. The remaining patient cleared by TEMLA was unfit for surgery.

In contrast, cervical mediastinoscopy found positive nodes in 3 of 20 patients and missed positive nodes that were subsequently detected in 5 of 15 cleared patients who went on to thoracotomy. Two other patients deemed node negative by mediastinoscopy did not undergo thoracotomy, one being unfit for surgery and the other refusing surgery.

Dr. Kuzdzal, a thoracic surgeon at the Pulmonary Hospital in Zakopane, Poland, and his Polish colleagues concluded that TEMLA's sensitivity and its negative predictive value were both 100%. They calculated a sensitivity rate of 66.7% and a negative predictive value of 37.5% for cervical mediastinoscopy.



**TEMLA is more effective because it is more thorough than cervical mediastinoscopy.**  
DR. KUZDZAL

Based on these results, the investigators stopped the randomized controlled trial, which had been scheduled to enroll 100 non-small cell lung cancer (NSCLC) patients. Dr. Kuzdzal said the hospital also has abandoned cervical mediastinoscopy for staging NSCLC because it missed metastases in 25% of patients in the mediastinoscopy arm of the trial.

“TEMLA is the standard technique for staging all potentially at-risk patients [at the hospital],” he said in a plenary address at the meeting, which was held with the European Society of Thoracic Surgeons.

Dr. Kuzdzal's coauthors included TEMLA's creator, Dr. Marcin Zielinski, head of the department of thoracic surgery in Zakopane. They published a description of the technique last year (Eur. J. Cardiothorac. Surg. 2005;27:384-90).

TEMLA is more effective because it is more thorough than cervical mediastinoscopy, according to Dr. Kuzdzal. The older procedure takes biopsy samples from five stations of the mediastinum. TEMLA completely excises lymph node stations 1, 2R, 2L, 3A, 3P, 4R, 5, 6, 7, and 8 plus the proximal 4L nodes using a limited cervical incision. On average 43.3 lymph nodes are removed.

TEMLA also takes considerably longer than cervical mediastinoscopy: 161 minutes vs. 68 minutes. “It is time consuming but lung cancer is a very disastrous illness and, if we are able to increase the chance for our patients of better treatment, I think these 2 additional hours are a relatively low price for it,” Dr. Kuzdzal said in an interview at the meeting.

“Our aim is to save the lives of our patients, not our time. The time is of secondary importance,” he added, describing the invasiveness of the procedure as low.

Associated morbidity was “not significantly greater” than with cervical mediastinoscopy, he said. Patients staged with by TEMLA had higher pain intensity scores, but both groups made similar use of analgesics.

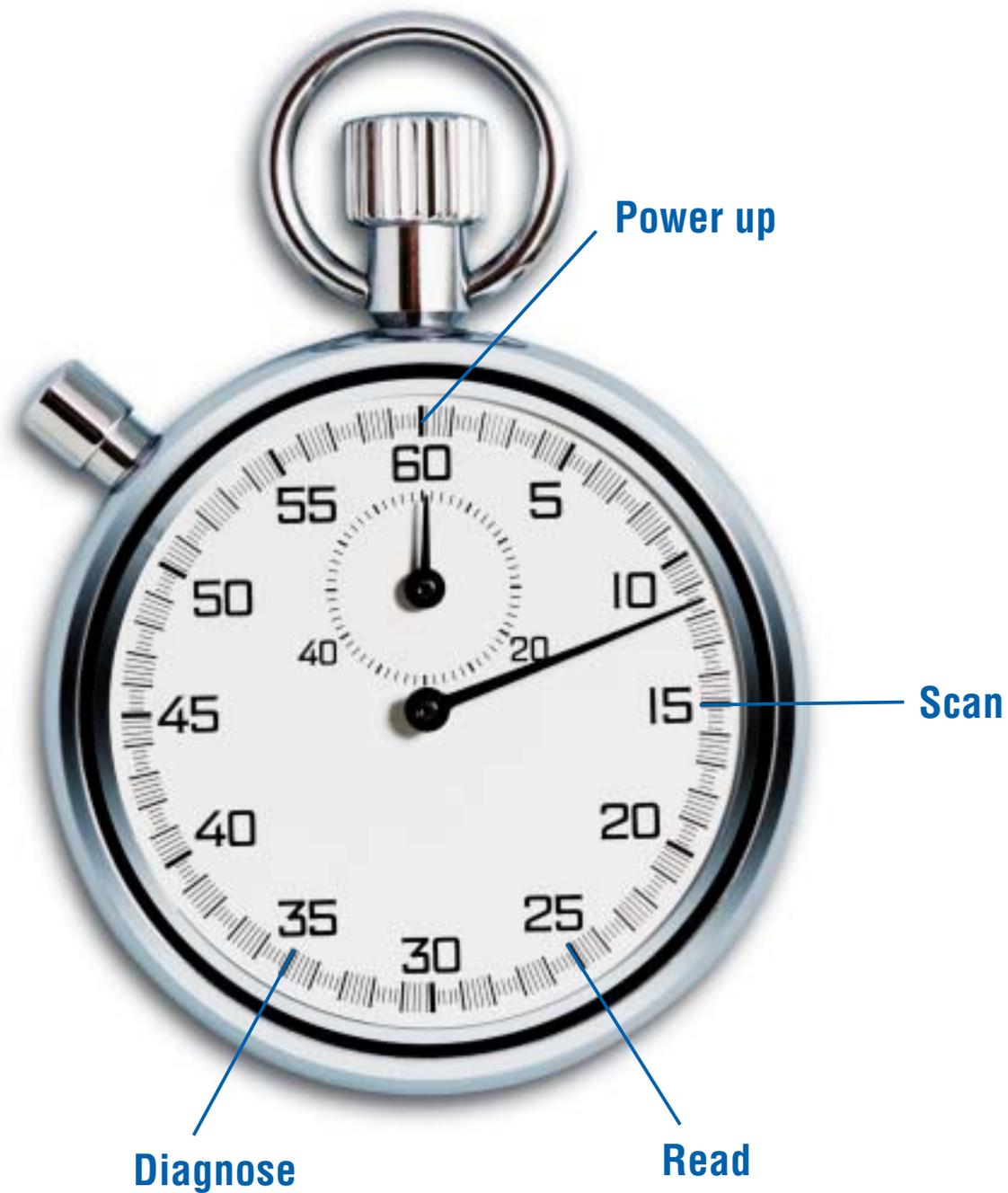
The investigators also examined pulmonary function because of concern that the new procedure might cause respiratory impairment and make patients unfit

for surgery. Dr. Kuzdzal said they found neither more impairment nor more unfit patients with TEMLA.

“The TEMLA procedure does not produce greater changes in lung ventilation nor gas diffusion across the alveolar-capillary membrane, compared to standard mediastinoscopy,” he said in a separate presentation on pulmonary function.

Ultimately, the investigators are hoping that longer follow-up will reveal better survival in more than 220 patients so far staged with TEMLA. “We know this technique is superior to other techniques in terms of staging, but we also think it might have also a curative impact,” Dr. Kuzdzal said. ■

**Dr. Robert Cerfolio, FCCP, comments:** Although transcervical extended mediastinal lymphadenectomy is a promising technique, the risk of the procedure may be too high in nonexperienced hands. Since the vast majority of lung cancer surgery is performed by surgeons who have “low volume experience,” and because more than 50% of mediastinoscopies yield no lymph nodes, the emphasis should be on training surgeons on how to perform standard mediastinoscopy. Then EUS-FNA, EBUS, and other types of procedures can be used to biopsy lymph nodes that have been targeted by integrated PET/CT.



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# Reflux May Trigger Cough in Some Asthmatic Children

BY DAMIAN McNAMARA  
Elsevier Global Medical News

ORLANDO — Reflux prompted coughing for more than a third of pediatric patients with asthma in a study, suggesting both acid and nonacid reflux can be important triggers for some patients.

Multiple studies suggest an association between often-undetected gastroesophageal reflux and asthma symptoms in adults; data in children are fewer.

However, treatment of reflux with a proton pump inhibitor (PPI) did not improve asthma symptoms in two large adult studies or one prospective pediatric study.

"We know [an association between] asthma and reflux is a long and ongoing saga, but we didn't know which was causing which," Dr. Devendra Mehta said in an interview during a poster presentation at the annual meeting of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

Use of pH monitoring alone—which detects only acid reflux—was a limitation of previous studies, he said. Impedance monitoring improves detection by including nonacid reflux episodes.

"With newer technology, we can now

see the stomach contents coming up and time it with the cough," said Dr. Mehta, a gastroenterologist at the Nemours Children's Clinic in Orlando.

Dr. Mehta and his colleagues assessed reflux in 87 children with asthma using combination pH and multichannel impedance monitoring. The mean age of the study participants was 7 years (range, 6 months to 18 years), and 49 were male. The researchers excluded candidates who were taking acid-suppression medications, and then studied 59 remaining patients.

A total of 38% of cough episodes occurred within 2 minutes of reflux, in about the same proportion following acid, weak acid, and nonacid reflux.

The cough episodes did not vary significantly by patient age or asthma severity.

"We are zeroing in on this population where reflux is causing an important part of the illness," Dr. Mehta said.

"The next phase will be treatment of these children with combined therapy to

see if we can help their asthma or keep it from getting worse," he said.

Dr. Mehta suggested a combination trial of a PPI and a motility agent for patients whose asthma does not improve with other therapies, to detect any concomitant reflux.

**IN ALL, 38% OF COUGH EPISODES OCCURRED WITHIN 2 MINUTES OF REFLUX, IN ABOUT THE SAME PROPORTION AFTER ACID, WEAK ACID, AND NONACID REFLUX.**

"We want to start out with younger kids to prevent them from a long course of lung problems," Dr. Mehta said.

Gastroesophageal reflux may trigger asthma symptoms by first causing microaspiration,

which then leads to edema, inflammation, and bronchial hyperactivity, Dr. Colin Rudolph said during another presentation at the meeting.

Evidence supports reflux as a potential contributor to severe, persistent asthma, said Dr. Rudolph, a pediatrician at the gastroenterology clinic of Children's Hospital of Wisconsin, in Milwaukee.

However, "evidence does not support a reflux prescription in all patients with persistent asthma who fail [conventional therapies]," Dr. Rudolph said.

He cited two double-blind, placebo-controlled studies that assessed PPI treatment of reflux in adults with asthma. Peak expiratory flows of adults treated with esomeprazole improved only for the subset that experienced nocturnal respiratory symptoms (*Am. J. Respir. Crit. Care Med.* 2006;173:1091-7).

"So a trial of PPI therapy should be considered reasonable in patients with [gastroesophageal reflux] symptoms and moderate to severe asthma," Dr. Rudolph said, "but efficacy may only be expected in patients who have nocturnal asthma symptoms."

In another study of adults treated with lansoprazole, there was no significant improvement in symptoms of asthma or pulmonary function (*Chest.* 2005;128:1128-35).

Only one set of researchers assessed treatment of reflux in pediatric patients with asthma in a prospective, randomized fashion, Dr. Rudolph said.

In that study, although omeprazole failed to improve the symptoms of asthma or lung function among a group of 38 children, the researchers "found that the PPI improved quality of life for the treatment group" (*Arch. Dis. Child.* 2005;90:956-60). ■

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Sleep Medicine Board  
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AMERICAN COLLEGE OF  
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## NEWS FROM THE COLLEGE



BY DR. MARK J. ROSEN, FCCP

## PRESIDENT'S REPORT

## Partnering To Shape Our Profession

The ACCP's mission is to promote the prevention and treatment of disease through leadership, education, research, and communication, and working with like-minded organizations is critical to supporting that mission. Among our most gratifying accomplishments in the last few years has been developing close collaborative relationships with other professional organizations, such as the strong and coordinated advocacy effort to influence public policy on the critical care workforce shortage by ACCP, the American Association of Critical-Care Nurses (AACN), American Thoracic Society (ATS), and Society of Critical Care Medicine (SCCM).

Training pathways and requirements for certification in pulmonary, critical care, and sleep medicine are also of great importance to our members, our profession, and the general public. The ACCP has forged strong partnerships with other organizations to shape how our profession evolves in response to rapid changes in educational methodology, informatics, and the drive to improve and document quality of care.

The ACCP now has several areas of collaboration with the American Board of Internal Medicine (ABIM), the US board that sets the standards and certifies the knowledge, skills, and attitudes of physicians who practice in internal medicine and its subspecialties.

Through its Certification and Maintenance of Certification (MOC) programs, successful candidates are awarded or maintain "board-certified" status. This demonstrates to the public that they have successfully completed a rigorous educational and evaluation process designed to assess the knowledge, experience, and skills required to provide high-quality patient care. In addition, MOC programs foster lifelong learning and a commitment to improving clinical practice.

To its great credit, ABIM elicits input enthusiastically from professional societies about the content and processes of certification, and the ACCP is committed to all of these activities. The College has participated in every ABIM Liaison Committee for Recertification

meeting, offering ACCP views on the appropriate requirements for MOC, along with providing source material to ABIM for pulmonary and critical care clinicians to fulfill these requirements with a Performance Improvement Module in asthma care.

**THIS COLLABORATION AMONG SOCIETIES IS THE MOST CONSTRUCTIVE AND EFFECTIVE WAY TO HAVE A POSITIVE IMPACT ON OUR PROFESSION.**

ABIM requires completion of self-evaluation modules to demonstrate medical knowledge and encourage learning, and ACCP was the first organization to offer ABIM module-based sessions at its annual meeting and board review courses; they have been a standard feature of these courses since 2002. We are developing online modules based on ACCP-SEEK that will allow candidates to complete 20 "learning" points for pulmonary and critical care medicine, respectively. These may be used instead of the traditional ABIM Self-Evaluation Process (SEP) modules.

The ABIM recently changed the "official" status of Critical Care Medicine by recognizing it as a subspecialty rather than an "added qualification." Physicians with certificates in critical

care medicine and geriatric medicine are no longer required to maintain their certificate in internal medicine to participate in the MOC program, although they are encouraged to do so.

To further define the field of critical care, ABIM charged a "critical care stakeholders" group to advise them on specifying the competencies of subspecialists in pulmonary and critical care medicine. In this exciting new effort, representatives of ACCP, ATS, SCCM, and the Association of Pulmonary and Critical Care Program Directors are now charting the future of subspecialty training by defining the domains of knowledge and the ways to demonstrate competency required to be certified as a subspecialist.

This collaboration among societies is surely the most constructive and effective way to have a positive impact on our profession. It should also be important for each of us as people: if not now, then all of us, our families and our friends will be patients, and we will all eventually have a critical illness.

We now have the opportunity to work with our colleagues to influence what we expect our own doctors to know and how we expect them to act. We have to do it right, and working with our colleagues, I am confident that we will. ■

## CHEST Rated #1 Journal by Pulmonologists

BY JENNIFER STAWARZ  
Senior Manager,  
ACCP Public Relations

For more than 70 years, *CHEST*, the premier journal of the American College of Chest Physicians, has been delivering the most advanced research in clinical chest medicine to medical professionals around the world. Although ACCP members have long recognized the value of the journal, new research confirms just how valuable *CHEST* is to pulmonologists.

"Now more than ever, new and experienced clinicians rely on *CHEST* for its cutting-edge research, evidence-based guidelines, and thought-provoking editorials, all of which have helped establish *CHEST* as the most widely read pulmonary, critical care, and sleep journal in the world," said *CHEST* Editor in Chief Dr. Richard S. Irwin, FCCP.

In a recent survey of 1,200 pulmonologists randomly selected from the American Medical Association membership roster, over 94% of the 256 pulmonologists who responded listed *CHEST* as a journal they receive and read, while 88%

consider it to be an "essential" journal. No other journal scored as high, with the next closest journal named "essential" by only 55% of respondents.

In addition, over 90% of pulmonologists consider *CHEST* a valuable resource for providing the latest information, expert opinions, and useful reviews, as well as information that influences their professional decisions.

"*CHEST* has always adhered to the highest standards of research reporting and expert commentary," said *CHEST* Executive Editor Stephen Welch, Vice President of Publications and Editorial Resources, American College of Chest Physicians. "Our readers acknowledge this dedication to quality and confirm their confidence in the journal by using the information to make the most informed decisions involving patient care."

With a rich history, grounded on the principle of education, the journal continues to evolve to meet the needs of an ever-changing global medical community.

The journal was first published in 1935 under the name *Diseases of the Chest*, with the purpose of

providing information and education primarily about tuberculosis (TB). As the rate of TB occurrences decreased in the United States, *CHEST* began focusing on other areas of growing concern.

To reflect the more multidisciplinary nature of chest medicine, the journal changed its name to *CHEST* in 1970 and expanded to include articles from pulmonary, critical care, sleep, and cardiovascular medicine.

In January 2006, the journal began a new era and welcomed a new editor in chief, modernized its cover, redesigned the table of contents, and implemented a more stringent acceptance process for submitted manuscripts.

Remaining true to its heritage, the journal still provides the latest research to its readers but also has become more reflective of contemporary societal issues and the practice of medicine.

The journal's new features will help readers apply basic research to clinical practice, learn more about medical ethics, understand how to run a medical practice, and improve their medical writing.

*Continued on following page*

## CHEST Facts

## Impact Factor and Citations

Impact Factor: 4.008  
Impact Factor Rank: 3rd of 33 in respiratory journal category  
Journal Citation Report: *CHEST* is 2nd of 33 journals in total citations

## Circulation

Largest circulation of any respiratory, critical care, or sleep journal in the world:  
► Members and subscribers: 20,450  
► International editions: 37,700

## Editorial Profile

Time to First Decision: 17 days  
Acceptance to Publication: 4 months (will drop in 2007 with Papers in Press advance online publication)  
Acceptance Rate: ~13% overall; 9% for original research  
Manuscripts: Received 3,368 in 2005, will receive 3,000+ in 2006  
Manuscripts Published by Geographic Region: 43% from United States, 5% from Canada, 52% from rest of the world

## Advertising Statistics

*CHEST* is #1 in market share, ad pages in respiratory, critical care, and sleep fields

## NETWORKS: MRSA Infections; CHEST 2007 Planning

### Chest Infections

BY DR. KELLY WOOD, FCCP

MRSA infections in the ICU pose significant challenges to pulmonary and critical care physicians. A significant rise in community-acquired MRSA is being reported. These include reports from neonatal intensive care units (*Pediatr Infect Dis J* 2006; 25:557; *Pediatr Infect Dis J* 2005; 24:1122) and cases of soft tissue infections (*N Engl J Med* 2005; 352:1445). Efforts must be made to minimize the selection and spread of these genetically distinct organisms in our ICUs. The indiscriminate use and overuse of antibiotics in the care of agricultural and domesticated animals must be examined in conjunction with similar practices in humans in order to understand all potential facets of this problem.

Most emerging infectious diseases in the world are zoonotic. From 1996 to 2004, 21% of 10,490 reports of animal diseases from 191 countries submitted to the Program

for Monitoring Emerging Diseases (ProMED) concerned humans affected by zoonotic disease (*J Am Vet Med Assoc* 2006; 229:1090). Due to the use of antibiotics to treat animals, agricultural animals have long been known to be a source of resistant bacteria. A Dutch study demonstrated transmission of MRSA between an

animal and human (pig and pig farmer), between family members (pig farmers and their families), and between a nurse and patient in the hospital (*Emerg Infect Dis* [serial]. 2005 Dec [date cited]. Available at [www.cdc.gov/ncidod/EID/vol11no12/05-0428.htm](http://www.cdc.gov/ncidod/EID/vol11no12/05-0428.htm).

Medical and veterinary personnel

should appreciate that animals can carry MRSA, and transmission between humans and domestic animals, although not common, can occur. Cats may serve as reservoirs for MRSA infections in humans (*Am J Vet Res* 2006; 67:1421; *J Sm Anim Prac* 2004; 45:591). MRSA has also caused infections in dogs (*Vet Rec* 1999;

### CHEST Is Rated #1

Continued from previous page

"CHEST is above all a clinical journal, with a very important educational mission," said Dr. Irwin. "The recent editorial changes illustrate the goal of improving the quality of research, scholarly works, and educational offerings published in CHEST."

Recent international initiatives and technological advances have helped make CHEST accessible to more readers across the globe.

CHEST has a print circulation of 20,450, reaching more than 100 countries, which is the highest of any medical journal in the respiratory, critical care, and sleep fields.

In its quest to expand medical knowledge beyond the English-speaking world, the ACCP publishes CHEST editions in Spanish, Italian, Turkish, and Chinese, and it also publishes an English edition in India; there are currently almost 38,000 recipients of these international editions.

For more information about the journal CHEST, please visit the journal Web site at [www.chestjournal.org](http://www.chestjournal.org).

The survey was commissioned by The Walchli Tauber Group, Inc., advertising representatives for CHEST, and fielded by The Matalia Group, Inc. To ensure a high quality study, readership was measured on a totally unaided basis, and the sponsorship of the study was not disclosed to respondents.

# THE POWER TO



## A UNIQUE SMOKING CESSATION THERAPY

- Dual action—agonist and antagonist effects at  $\alpha_4\beta_2$  nicotinic acetylcholine receptors

CHANTIX™ (varenicline) is indicated as an aid to smoking cessation treatment in adults.

Safety and efficacy of CHANTIX in combination with other smoking cessation drug therapies have not been studied.

Zyban is a registered trademark of Glaxo Group Limited.

**References:** 1. CHANTIX [package insert]. New York, NY: Pfizer Inc; May 2006. 2. Center for Drug Evaluation and Research. Approval package for: application number NDA 21-928: statistical review(s). Food and Drug Administration Web site. Available at: [http://www.fda.gov/cder/foi/nda/2006/021928\\_s000\\_Chantix\\_StatR.pdf](http://www.fda.gov/cder/foi/nda/2006/021928_s000_Chantix_StatR.pdf). Accessed August 25, 2006. 3. Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an  $\alpha_4\beta_2$  nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47-55. 4. Jorenby DE, Hays JT, Rigotti NA, et al, for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an  $\alpha_4\beta_2$  nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.

[www.chantix.com](http://www.chantix.com)

Please see brief summary of Prescribing Information on adjacent page.

# NEWS FROM THE COLLEGE



144:60; *Vet Rec* 2004; 154:11). Cases of human-to-dog transmission of MRSA, in which dogs have acted as reservoirs for reinfection, have been reported (*Clin Infect Dis* 2003; 36:e26).

Although it is not yet clear whether animal to human transmission of



MRSA has resulted in a significant number of new disease cases, the current state of antimicrobial resistance demands collaborative research between medical and veterinary personnel in order to control resistance and prevent transmission. In 2006, we saw the establishment of

the Centers for Disease Control and Prevention (CDC) as a World Organization for Animal Health (OIE) Collaborating Center for Emerging and Reemerging Zoonoses. This served as an initiative by health and animal organizations to respond to emerging zoonotic diseases that potentially impact human health. A forum was established to examine the epidemiology of pathogens and diseases shared by humans and animals, as well as

the effects of agricultural practices on humans ([www.cdc.gov/ncidod/EID/vol12no12/06-1281.htm](http://www.cdc.gov/ncidod/EID/vol12no12/06-1281.htm)).

### Allied Health

The Allied Health NetWork provides allied health professionals a method of communicating with all members of the ACCP. The membership of the

*Continued on following page*

# HELP THEM QUIT

**QUIT RATES SUPERIOR TO ZYBAN® AT 12 WEEKS IN HEAD-TO-HEAD CLINICAL TRIALS (P=.0001)<sup>1,2\*</sup>**

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

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

## WELL-STUDIED TOLERABILITY AND SAFETY PROFILE

- The most common adverse events associated with CHANTIX were nausea, sleep disturbance, constipation, flatulence, and vomiting
- Nausea was reported by approximately 30% of subjects treated with CHANTIX 1 mg bid, with approximately a 3% discontinuation rate during 12 weeks of treatment

## GET SUPPORT PLAN

- A personalized behavioral support program developed by experts specifically for your CHANTIX patients

**TURN MORE SMOKERS INTO QUITTERS**

**CHANTIX™**  
(varenicline) TABLETS

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

Subjects were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each clinic visit in accordance with Agency for Healthcare Research and Quality guidelines.<sup>1</sup>



# NEWS FROM THE COLLEGE

Continued from previous page

NetWork includes respiratory care practitioners, physician assistants, nurses, physical therapists, and pharmacists, as well as physicians.

The Airways, Allied Health, Respiratory Care, and Home Care NetWorks recently coordinated efforts and developed patient instructions for the use of inhaled aerosol devices. These step-by-step instructions

provide patients and physicians information on usage and cleaning for most delivery devices available today. These are available for download at: [www.chestnet.org/patients/guides/inhaledDevices.php](http://www.chestnet.org/patients/guides/inhaledDevices.php). A project such as this provides the physician and allied health practitioner tools to improve the management of lung disease. Another example of the importance of the Allied Health NetWork is its contribution to the update on sleep-disordered breathing for

the 2007 *Appropriate Coding for Critical Care Services and Pulmonary Medicine*.

The NetWork relies on its members to provide ideas for topics and presentations at the annual CHEST meetings and should be well represented at CHEST 2007, with proposals for three NetWork Highlights and three general session topics under review.

Interested in becoming involved? Contact [networks@chestnet.org](mailto:networks@chestnet.org).

## Cardiovascular Medicine and Surgery

The CVMS NetWork held its first business meeting since becoming the Cardiovascular Medicine and Surgery NetWork earlier in 2006. The meeting featured a talk by Dr. David Bull, from the University of Utah, on "Cells and Genes: The Next Wave of Cardiovascular Therapeutics."

The 2006 year was marked by 20 curricular sessions at CHEST 2006, covering a range of topics, including endothelial function, lipid management, heart failure, cardiogenic shock, plaque-independent ischemia, cardiovascular diagnostics, management of myocardial infarction, cardiac surgery variables affecting outcome, surgical perspectives on atrial fibrillation, perioperative cardiac risk assessment, cardiac biomarkers, as well as cardiology and cardiac surgery case reports and posters.

NetWork members have been active in other College activities, including representation of the College for evidence-based guideline reviews (echocardiography, ACS/AMI, atrial fibrillation). A NetWork-organized review paper on secondary hypertension is also nearing completion.

In preparation for CHEST 2007, the NetWork has submitted three NetWork Highlight topics and 25 general sessions for consideration by the program committee, covering a wide range of clinically-relevant topics. Installed as Network Chair at CHEST 2006, Dr. Stephen Geraci, FCCP, expressed his vision for the NetWork for the next 2 years: to grow NetWork membership and member participation, expand participation from cardiology fellows and residents, and focus our efforts on meeting the needs of the members of the College by concentrating educational programs in critical care cardiology and cardiovascular surgery.

The NetWork leadership warmly welcomes ideas and suggestions and invites all those wishing to become more involved in CVMS activities to contact Dr. Geraci (Chair), Dr. Thomas Behrenbeck, FCCP (Vice-Chair), or any steering committee member. E-mails can be sent to the NetWork at [networks@chestnet.org](mailto:networks@chestnet.org).

## Now Showing on chestnet.org

### Pulmonary Vascular Disease

Clinical experts in pulmonary vascular disease developed this up-to-date curriculum on several topics, including acute PE, PAH, and more.

Visit [www.chestnet.org/networks/pvd/curriculum.php](http://www.chestnet.org/networks/pvd/curriculum.php).

## CHANTIX<sup>TM</sup> (varenicline) TABLETS



Before prescribing, please consult Full Prescribing Information.

### INDICATIONS AND USAGE

CHANTIX is indicated as an aid to smoking cessation treatment.

### PRECAUTIONS

**General.** Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered. **Effect of smoking cessation:** Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

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

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

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

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

**Pregnancy.** Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). **Nonteratogenic effects.** Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended human daily exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers.** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Labor and delivery.** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use.** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use.** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given OD 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 dose 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
<b>GASTROINTESTINAL</b>			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain*	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4

(Table 3 continued)

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

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

\*\* Includes Pts Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

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

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

### DRUG ABUSE AND DEPENDENCE

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

### OVERDOSAGE

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

### DOSAGE AND ADMINISTRATION

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

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

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

### Special Populations

**Patients with impaired renal function.** No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal Impairment). **Dosing in elderly patients and patients with impaired hepatic function.** No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See PRECAUTIONS, Geriatric Use). **Use in children.** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Rx only

May 2006, Version LAB-0327-2.0

# NEWS FROM THE COLLEGE



## THE ACCP INSTITUTES 2006 Year in Review: Collaboration and Progress

BY MICHAEL BOURISAW  
Director of ACCP Institutes

In 2006, the ACCP Institutes were recognized as important partners in the arenas of sleep and critical care medicine. Both Institutes made strides by working collaboratively on projects that are important to their respective fields. Some of the key projects of the Institutes, as well as areas of future interest, are presented below.

### The American College of Chest Physicians Critical Care Institute (ACCP-CCI)

The ACCP-CCI, under the stewardship of Chair Dr. Curt Sessler, FCCP, and the rest of the steering committee, has tackled several areas in critical care that were important, timely, and that required a multidisciplinary approach to best address the issues involved.

In March, a team of experts in critical care, palliative care, and pain management was assembled to discuss the issue of unmanaged pain in the ICU. This multidisciplinary approach uncovered many incidents of unrecognized and unmanaged pain that occur daily in patients in the ICU.

The goal of the group is to eliminate or mitigate those occurrences. That initial workshop has led to the publication of a summary article in *CHEST Physician* (October 2006) and an excellent multidisciplinary panel discussion at CHEST 2006.

Next up for this group will be the creation of practical tools for the members of the care delivery team, as well as submission of a comprehensive review article to *CHEST*.

The ACCP-CCI is also working with colleagues in pharmacy and nursing on the creation of a pocket guide for health-care workers that will provide basic information on commonly used medications in the ICU. That project is close to being finalized and will be brought to fruition through a collaborative venture with the International Guidelines Center.

Together with The CHEST Foundation, the ACCP-CCI has emphasized the outstanding Critical Care Family Assistance Program (CCFAP). The ACCP-CCI is focusing its efforts on increasing dissemination and implementation of the CCFAP. Several opportunities were developed and were completed or continue to be pursued.

In April, a presentation was given to member organizations of VHA Inc., a hospital buying group that represents over 1,000 health-care organizations.

This was followed by conference calls in June and August to monitor the progress of 15 institutions that purchased and were implementing the CCFAP.

In June, a joint effort with Evanston Northwestern Healthcare resulted in the creation of a storyboard that was presented at the Institute for Healthcare Improvement conference in Atlanta, GA, with an attendance of several thousand health-care workers.

Finally, an effort by Dr. Peter Spiro, FCCP, an ACCP-CCI steering committee member, has resulted in discussions with NYC Health and Hospitals Corporation about the implementation of the CCFAP in its 15 member institutions. We will continue our efforts to

expand the impact of the CCFAP.

Another important project that has developed under the auspices

of the ACCP-CCI is focused on providing operational guidance and a systematic approach to the augmentation and allocation of critical care services in the event of an overwhelming mass casualty event, such as a pandemic flu outbreak.

This collaborative project has been under development over the last several months and is being led by a cross-functional team that includes critical care and disaster planning expertise from physician, nursing, pharmacy, respiratory care, and government sources, as well as legal and ethical expertise from individuals well versed in this area of interest. A working group met at CHEST 2006 and developed an outline that will form the basis of a more extensive group effort to be finalized in the first quarter of 2007.

The ACCP-CCI will continue to look at areas in critical care medicine that are important to our members, some requiring expertise and input that extend beyond the membership of the ACCP. Collaborative efforts continue to produce excellent outcomes.

### The American College of Chest Physicians Sleep Institute (ACCP-SI)

Sleep medicine continues to grow and evolve in the United States, and the ACCP-SI provides the ACCP a visible and active presence in the world of sleep medicine.

The Institute of Medicine report released in 2006 pointed to the importance of educating, diagnosing, and treating the millions of Americans with sleep disorders. The Chair, Dr. Charles Atwood, FCCP, and an active

steering committee, have enabled the ACCP-SI to develop or participate in a number of collaborative and worthwhile projects.

One such project involved bringing together representatives of a diverse group involved in the care of patients who have been diagnosed with obstructive sleep apnea (OSA). A working group of physicians, technicians, home health providers, manufacturers, payers, and patients used the nominal group process method to arrive at the crucial issues

that need to be addressed to provide consistent quality care to patients with OSA. A writing group will now use the agreed-upon items of importance to develop a consensus document for submission to *CHEST*. Further meetings should help establish set criteria that could be adopted by the various entities to provide continuity of care to the patient with OSA.

The ACCP-SI is developing and presenting a series of regional sleep education programs aimed at the primary care provider. An unrestricted educational grant from Boehringer Ingelheim enabled the ACCP-SI to start this series of 21 programs in December 2006. This began with the efforts of a content development group, including ACCP sleep

specialists and primary care providers involved in sleep medicine.

The scientific content developed results in a half-day program, featuring an evidence-based approach to common sleep disorders, such as OSA, restless legs syndrome, and insomnia. Thanks to materials provided by the National Sleep Foundation and our ACCP Education Division, each participant walks away

with a tool kit and a textbook directed toward primary care providers and their patients.

The enthusiastic response of the ACCP Sleep

NetWork members resulted in over 100 applicants vying to be a host site for a regional program.

The ACCP-SI is also involved in an important national sleep advocacy effort headed by the National Sleep Foundation and involving more than 30 private and public organizations. The National Sleep Awareness Roundtable will be focusing its efforts on ensuring that Americans understand the importance of healthy sleep through its joint efforts in public awareness and improved communication and collaboration.

The ACCP-SI will continue to seek out and collaborate with other organizations interested in all aspects of sleep medicine, as we seek to serve both our members and their patients. ■

## Pulmonary Perspectives

### Dr. Gene L. Colice, FCCP, Is New Editor Of Pulmonary Perspectives

We are pleased to announce that Dr. Gene L. Colice, FCCP, is the new Editor of *Pulmonary Perspectives*. Dr. Colice is Professor of Medicine at The George Washington University School of Medicine in Washington, DC. He is also Director of Pulmonary, Critical Care, and Respiratory Services at Washington Hospital Center in Washington, DC.



DR. GENE L. COLICE, FCCP

Dr. Colice currently is a member of the ACCP Bylaws and Quality Improvement Committees, Vice-Chair for the ACCP Diagnosis and Management of Lung Cancer initiative, and member of the

ACCP-SEEK writing committee for pulmonary. He has served as Chair of the ACCP Health and Science Policy Committee and as a member of the CHEST Program Committee and the Lung Cancer Steering Committee.

Dr. Colice is a member of the *CHEST* editorial board.

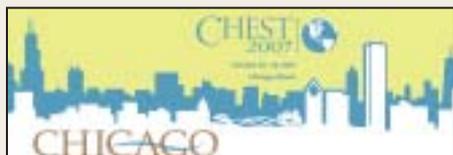
As Editor of *Pulmonary Perspectives*, Dr. Colice plans to "offer a forum for provocative opinions about items of current interest to the pulmonary community, not only from experts in the field, but from any member of the ACCP." ■

## CHEST 2007 Destination Is Second City to None

**K**nown to many as the "Second City," Chicago promises to be second to none

as the destination for CHEST 2007. Dynamic and captivating, Chicago is known for first-rate meeting venues and world-class entertainment options, making it the ideal meeting destination to combine business and pleasure.

Clinical education has always been the top priority at CHEST, and it will be again at CHEST 2007 in Chicago. You can attend relevant updates on patient care strategies and participate in diverse development opportunities for your professional growth. Most sessions will take place at McCormick Place, Lakeside Center, a state-of-the-art meeting facility, featuring unparalleled amenities to enhance your learning experience.



When you're ready for a break from the meeting, the "Second City" is full of top-rated options:

*Dine* on Chicago mainstays, like a perfect steak or deep-dish pizza.

*Hear* performances from the Chicago Symphony Orchestra, or visit a nightclub to hear blues or jazz.

*Appreciate* beloved works of art, just beyond the famous lion entryway, at the Art Institute of Chicago.

*Explore* the lakefront and its attractions. *Cheer* for your favorite Chicago team at a sporting event.

*Shop* the Magnificent Mile, Oak Street, or historic State Street.

Make plans now to attend CHEST 2007, October 20-25, in Chicago. Watch for more meeting details at [www.chestnet.org](http://www.chestnet.org).

## Practice Management Update

The ACCP needs your help. Have you had a desire to actively be involved in national coding and reimbursement issues? Are you interested in becoming an active member of the ACCP Practice Management Committee? Are you interested in the business side of medical practice? Are you detail oriented? Do you have e-mail and can you work with e-mailed attachments?

Then, the ACCP has a voluntary position that will suit your interests. The College has advisors and alternate advisors participating in the American Medical Association's CPT and RUC processes. As part of this responsibility, you would participate in the monthly ACCP Practice Management Committee conference call.

Requirements: ACCP and AMA memberships, and a desire to participate in national processes that affect the CPT codes you use and your future Medicare reimbursement.

Apply for this position by e-mailing

Marla Brichta at the address [mbrichta@chestnet.org](mailto:mbrichta@chestnet.org), with a short biographical sketch of your background to include: name, e-mail address, telephone number, specialty, and practice concentration. State any expertise that you have related to coding and reimbursement issues.

### Available Now

*Appropriate Coding for Critical Care Services and Pulmonary Medicine 2007*

New information you need to know for billing and reimbursement in 2007:

- ▶ New ventilation management codes
- ▶ 6-minute walk test and oximetry were added to the parenthetical for simple pulmonary stress testing.
- ▶ New code for expired nitric oxide
- ▶ New sleep apnea codes
- ▶ New code for surfactant administration for anticoagulant

For convenient ways to order, check the Coding Book ad in this issue.

## Clinical Pulmonary Updates...Sized for Kids



### CELEBRATION OF PEDIATRIC PULMONOLOGY 2007

March 16 - 18  
San Antonio, Texas

Co-Chairs  
LeRoy Graham, MD, FCCP  
Dennis Gurwitz, MB, BCh, FAAP  
Pedro Mayol, MD, FCCP

Plan now to attend this state-of-the-art update in clinical pediatric pulmonology to hear the latest research findings for topics in pulmonology, infectious disease, radiology, and surgery.

Designed to promote interaction between you and the renowned faculty, this course will allow you to:

- Hear recent clinical updates related to pediatric lung disease.
- Participate in interactive discussions and hands-on workshops with experts in the field.
- Ask questions about issues specifically impacting your practice.

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## Missed a Session at CHEST 2006?

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NEWS FROM THE COLLEGE



EDUCATION INSIGHTS

Why Did the Chicken Cross the Road?

BY ED DELLERT, RN, MBA  
Vice President, Educational Resources

“Because it was there,” correct? This age-old question has been contemplated for generations. Plato thought it was done for the greater good. Aristotle thought it was in the nature of chickens to cross roads. Captain James T. Kirk thought it was to boldly go where no chicken has gone before. What if, however, we were to replace this question with, “Why did the physician cross the road?” In today’s health care regulatory environment, with the need to measure “physician competency,” it seems that it might be an appropriate question to ask.

► **September 5, 2006:** The Accreditation Council for Continuing Medical Education (ACCME) released the latest update to the guidelines for providers of continuing medical education (CME). The focus upon the updated criteria is highlighted in the following three areas that state CME must:

1. Contribute to patient safety and practice improvement
2. Be based upon valid content
3. Be independent of commercial interests

These three areas are to be incorporated throughout the year into individual physician educational activities by the CME curriculum provider. The outcome of these learning experiences should demonstrate how the collective curriculum impacts the CME provider’s educational mission. Specifically, providers must begin to assess how educational experiences are facilitating physician learning and enabling a means to assess physician performance, competence, and clinical impact upon patient outcomes.

► **October 10, 2006:** A letter came from the office of the ACCME stating that the updated criteria are designed to align the goals of the CME providers with the goals of CME learners (ie, physicians). In today’s environment of health care, both parties are being asked to assess their abilities and demonstrate change and improvement. Medical education is being driven by professional practice gaps of physician learners, and needs are being expressed in terms of knowledge, competence, and/or performance changes, as it impacts upon professional practice. Success will be based upon “data.” Dr. James Thompson, President and CEO of the Federation of State Medical Boards of the United States, stated the following as it relates to the release of ACCME’s updated criteria:

“The new accreditation elements will prove to be valuable in the national initiatives to assure competence of physicians. This level of activity is just what has been needed to place the continuing medical education community at the forefront of improving quality in the practice of medicine.”

Implementation of the updated criteria is to begin

November 2008, with demonstration of 100% compliance by 2012. (See figure.)

► **November 16, 2006:** The US Council of Medical Specialty Societies (CMSS) hosts a 1-day summit discussing the use of physician’s self-assessment programs. Two Canadian researchers, Dr. David A. Davis, of the University of Toronto, and Dr. Kevin Eva, of the program for Educational Research and Development at McMaster University, highlighted their findings during their most recent research.

Dr. Davis highlighted his most recent article in the *Journal of the American Medical Association*, with the following findings:

1. CME credit, relicensure (revalidation), and recertification are linked to the abilities of physicians to assess their own needs and select learning activities to meet those needs.
2. In a literature search of comparisons between self and external assessment, 13 of 20 studies demonstrated little, no, or an inverse relationship; 7 demonstrated a positive association.
3. A number of studies found the worst accuracy in self-assessment among those who were the least skilled.
4. Conclusion: The preponderance of evidence suggests that physicians have a limited ability to accurately self-assess.

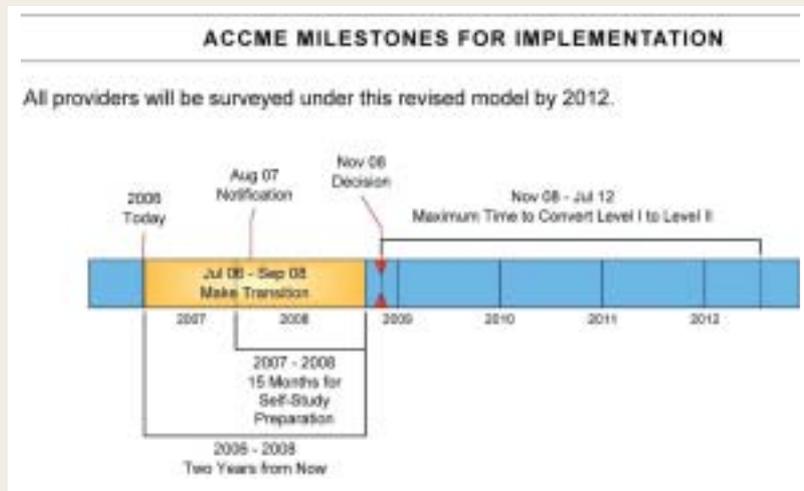
For more information on Dr. Davis’s article, go to the following URL: <http://jama.amaassn.org/cgi/content/full/296/9/1094>.

Dr. Eva concluded similar findings in an article he highlighted from the October 2005 supplement in *Academic Medicine*. He indicated the following:

1. The archetype of the self-regulating professional will reflect regularly on practice and self-assessment gaps, seek to redress these, and incorporate new knowledge and skills in practice.
2. All but the very highest performers tend to overestimate their ability.
3. Those most in need of improvement are those least likely to know.
4. Conclusion: A critical premise (self-assessment) underlying the concept of self-regulation is unsupportable.

For more information on Dr. Eva’s article, go to the Academic Medicine home page and search for the archive editions under the October 2005 supplement, entitled “Self-Assessment in the Health Professions: A Reformulation and Research Agenda” at [www.academicmedicine.org](http://www.academicmedicine.org).

Dr. Robert Galbraith, Director of the Center for Innovation of the National Board of Medical Examiners (United States), discussed the development of



practice or work profiles for individual physicians, linking these to multiple-choice questions to test knowledge competency, and, in turn, adding external assessment in the forms of comparison to practice norms and mentoring. These steps, he suggested, can assist physicians in demonstrating learning and performance improvement.

Highlights of the discussion also indicated that the US Federation of State Medical Boards is seeking to move from a mandatory credit-hour basis in most states to measurement of the ongoing competence of a physician. Many countries still have no relicensure requirements in place.

► **December 3, 2006:** In physics, “theory” is when you know how it works, but it still doesn’t. “Practice” is when it works, but you don’t know why. I think what has happened is that theory and practice have joined forces together, where nothing works, and no one knows why! The ACCP, however, is looking for tools in which the theory is how adults best learn. The practice is how best to teach adults and capture that learning process to determine knowledge competency and correlate it to individual clinical practice.

This entire discussion is not hot news to the ACCP Continuing Education Committee. This has been discussed over the past few years and has evoked many ideas on how the ACCP can best serve to meet these future demands of its constituency.

In 2007, these discussions will now lead to the implementation of a new Continuing Medical Education learning curriculum, and we hope it will transform teaching and learning in chest medicine. Our hope is to encourage ACCP membership participation by educating everyone about the need—and how that need will be met by participating in this new learning structure. This article is just the beginning of that educational process. So, why will you cross the road? Or will you?

As always, feel free to contact me for questions or comments on this article, at [edellert@chestnet.org](mailto:edellert@chestnet.org). ■

This Month in CHEST: Editor’s Picks

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

► **Antibiotic Treatment of Exacerbations of COPD: A Randomized, Controlled Trial Comparing Procalcitonin-Guidance With Stan-**

**dard Therapy.** Dr. Daiana Stolz, et al

► **Post-ICU Mechanical Ventilation at 23 Long-term Care Hospitals: A Multicenter Outcomes Study.** Dr. David J. Scheinhorn, FCCP, et al

► **Ventilator-Dependent Survivors of**



**Catastrophic Illness Transferred to 23 Long-term Care Hospitals for Weaning From Prolonged Mechanical Ventilation.** Dr. David J. Scheinhorn, FCCP, et al

► **Unexplained Pulmonary Hypertension in Elderly**

**Patients.** Dr. Brian P. Shapiro, et al

► **Wedge Resection vs Lobectomy:**

**10-Year Survival in Stage I Primary Lung Cancer.** Dr. Alexander Kraev, et al

► **Impaired Objective Daytime Vigilance in Obesity-Hypoventilation Syndrome: Impact of Noninvasive Ventilation.** Dr. Nathalie Chourri-Pontarollo, et al

[www.chestjournal.org](http://www.chestjournal.org)

# Creating Healthy Work Environments: Introduction

*The AACN and the ACCP are committed to safe, quality care.*

BY DENISE C. THORNBY, MS, RN, CNAAC;  
AND  
DR. CURTIS N. SESSLER, FCCP

Critically ill patients are our most vulnerable patients in health care and require the full contribution and skill of competent and caring physicians and nurses.

For decades, both professions have focused on the acquisition of knowledge and skills required for excellent patient care. Less attention has been traditionally placed on the “soft” skills of communication, collaboration, and creating work cultures that support effective teamwork.

There is a growing body of evidence pointing to links between effective nurse-physician collaboration

and improved outcomes (including reduced mortality rates) for patients, the adequacy of nurse staffing and patient outcomes, and the quality of the work environment with clinical performance.<sup>1</sup>

The Institute of Medicine (IOM), in *Crossing the Quality Chasm: A New Health System for the Twenty-First Century*, calls for a revolution in the way in which we communicate with each other, anticipate and modify patients’ risk, and evaluate our effectiveness.<sup>2</sup>

The leaders of the American Association of Critical-Care Nurses (AACN) and the American College of Chest Physicians (ACCP), who have a long history of collaboration and support on important issues in critical care, have committed to promote healthy work environments that foster safe, quality care. In 2005, AACN established six evidence-based, relationship-centered standards to cultivate healthy work and care environments<sup>3</sup>:

- ▶ Skilled communication
- ▶ True collaboration
- ▶ Effective decision-making
- ▶ Appropriate staffing
- ▶ Meaningful recognition
- ▶ Authentic leadership

These standards involve fundamental concepts in the way individuals on the health-care team relate and interact with one another. Promotion of these standards is crucial to ensure patient safety, decrease medical errors, improve delivery of care, and increase the retention of staff by decreasing conflict, stress, and moral distress among members of the health-care team.<sup>4</sup> The critical elements of the standards may be found on the AACN Web site at [www.aacn.org/HWE](http://www.aacn.org/HWE).

As physicians and nursing leaders in the care of the critically ill, it is imperative for us to consider strategic actions to transform the culture and work environment within our units and hospitals. How can you personally make an impact in your ICU and more broadly throughout your health-care system? Changing long-held biases and ingrained behaviors is challenging work that requires true collaboration among those who are leading the charge. Familiarize yourself with the AACN standards and consider the

implementation strategies identified by authors of the article, *One Year after the AACN Standards: Where we are now?*<sup>4</sup> Additionally, articles in this and subsequent issues of *CHEST Physician* by physician and

nurse leaders will provide valuable insight and personal experience for successful implementation of each of the individual standards. We must all strive to establish and sustain healthy work environments—our patients’ health and

our professional well-being depend upon it.

Watch for future articles in *CHEST Physician* on the Healthy Work and Care Environments initiative. ■

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1. McCauley K, Irwin RS. Changing the work environment in ICUs to achieve patient-focused care: the time has come. *Chest* 2006; 130:1571-1578
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4. Cassidy L, Barden C. One year after the AACN standards: Where are we now? *AACN Adv Crit Care* 2006; 17:119-124

MS. THORNBY is Director, Education & Professional Development, Virginia Commonwealth University Health System, Richmond, VA. DR. SESSLER is an Orhan Muren Professor of Medicine, Virginia Commonwealth University Health System, and Medical Director of Critical Care, Medical College of Virginia Hospitals, Richmond, VA.

## Steps Toward Creating a New Environment

### ▶ Start with a self-assessment.

Looking honestly at one’s own contribution to the work environment and the kind of influence it has.

### ▶ Assess the environment and “culture” within your unit.

Those who work in a unit are the ones who create and reinforce acceptable culture. Observe and reflect upon the reality and compare with the elements of the six critical elements from the AACN HWE standards.

### ▶ Develop an action plan.

Develop a well-articulated clear plan of action. Encourage the involvement of all in the plan and its actions. Focus on the standards most in need of attention.

### ▶ Stay the course.

Change of this magnitude will take time, patience, and long-term commitment. It is a continual journey.

## CHEST Physician Welcomes New Editorial Advisory Board Members



CHEST Physician is pleased to introduce our readers to the newest members of our editorial advisory board.

**Dr. Doreen Addrizzo-Harris, FCCP**, (not pictured) is Associate Professor of Medicine at NYU School of Medicine,

Program Director of the Pulmonary-Critical Care Medicine Fellowship, and Section Chief of Pulmonary at Tisch Hospital, New York.

Dr. Addrizzo-Harris is an ACCP Governor for New York City and presently serves on the Health and Science Policy Committee and the Government Relations Committee.

**Dr. Stephen A. Geraci, FCCP**, is Professor and Vice-Chair, Department of Internal Medicine, University of Mississippi School of Medicine, and Chief of the Medical Service, G.V. (Sonny) Montgomery VA Medical Center, Jackson, MS.

Dr. Geraci is Chair of the ACCP Cardiovascular Medicine and Surgery NetWork and serves on the CHEST 2007 Scientific Program Committee.



DR. STEPHEN A. GERACI,  
FCCP

**Dr. Stephen M. Pastores, FCCP**, is Associate Attending Physician and Director of the Critical Care Medicine Fellowship program at Memorial Sloan-Kettering Cancer Center in New York, NY, and Associate Professor of Medicine and Anesthesiology at Weill Medical College of Cornell University.

Dr. Pastores is a member of the Association of Pulmonary and Critical Care Medicine Program Directors and the steering committee of the ACCP Cardiovascular Medicine and Surgery NetWork.



DR. STEPHEN M. PASTORES,  
FCCP

# CHEST 2006 WRAP-UP



## CHEST 2006—A Meeting of Minds, Mountains, and Moments

BY PAM GOORSKY

Assistant Vice President, Editorial Resources

They arrived in Salt Lake City—thousands of physicians and their teams, their colleagues, and their families. They arrived from more than 60 countries. They arrived to lecture, to listen, and to learn. And they arrived with great expectations of an educational event that would provide new knowledge that could be applied immediately in their practices here in the United States and around the globe.

CHEST 2006 met and exceeded those expectations, offering 6 days packed with education, simulation, collaboration, and just plain fun. With more than 200 educational opportunities, ranging from mini-satellites to literature reviews to a ballroom-filled keynote session, CHEST 2006 provided a nonstop, unmatched educational venue. Having 30 curriculum categories from which to choose, attendees enjoyed the advantages of the multidisciplinary nature of CHEST. The ACCP Networks offered 26 open meetings, so attendees could choose one or more to enjoy special presentations geared to particular interests.

Collaborative meetings with national and international organizations allowed ACCP leaders to share and discuss mutual goals with others of similar

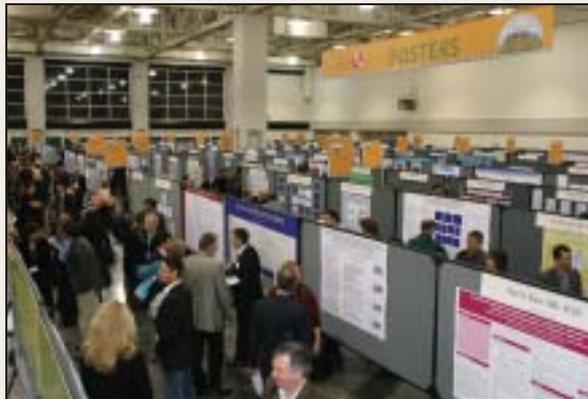
interests. A record-breaking number of exhibits furnished important information on new pharmaceuticals, equipment, and technologies. Numerous ACCP and CHEST Foundation honors and awards graced the Convocation ceremony and the Wednesday evening awards reception.

And what would a CHEST meeting be without The CHEST Foundation's Making a Difference Dinner? Or the opening reception? Or a night of special reunions to meet and greet friends and colleagues?

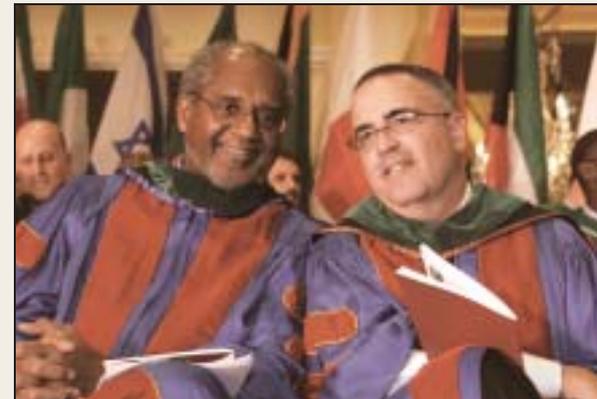
These traditional events and many more were met with enthusiasm and wonderful crowds.

CHEST 2006 provided its more than 4,000 attendees with a scientific meeting having unlimited possibilities for learning, a beautiful geographic area to explore, and an opportunity to network and catch up with friends.

Join us for CHEST 2007 in Chicago, and once again experience the ACCP heritage of educational excellence.



More than 450 research posters were presented at CHEST 2006.



ACCP President-Elect Dr. Alvin V. Thomas, Jr., FCCP, and President Dr. Mark J. Rosen, FCCP, share an anecdote.



## call for abstracts

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- **Receive feedback** from the clinicians likely to use your data in their practices. Health-care professionals in chest and critical care medicine will review and comment on your work.
- **Participate with the ACCP in efforts to fight chest diseases.** By presenting your findings, you join the ACCP in its mission to advance the prevention and treatment of chest diseases through research and education.
- **Compete for ACCP investigative awards.** Monetary awards are granted by The CHEST Foundation to investigators whose work is judged to be outstanding by the reviewers.

**Abstract submission to CHEST 2007 is FREE.** Domestic and international submissions are encouraged. Abstracts will be graded individually on scientific merit and originality. Abstract submission begins early March. Submit online at [www.chestnet.org](http://www.chestnet.org) by clicking on the Abstracts and Case Reports Submission link when available. For questions, call (800) 343-2227 or (847) 498-1400.

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- Identifies and advances the best delivery of medical education.

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## CHEST 2006 Award Winners

### ACCP Honor and Memorial Lecturers and Awardees

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Dr. Harry R. Kimball

#### Honorary Fellow Award

The Honorable Senator Mike Crapo, FCCP (Hon)

#### Presidential Citation Honor Lecture

Dr. Stuart M. Brooks, FCCP

#### Roger C. Bone Memorial Lecture

Dr. Michael A. Matthay, FCCP

#### Murray Kornfeld Memorial Founder's Lecture

Dr. Michael D. Iseman, FCCP

#### Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation

Dr. Allen I. Goldberg, Master FCCP

#### Pasquale Ciaglia Memorial Lecture in Interventional Medicine

Dr. John F. Beamis, FCCP

#### Edward C. Rosenow III Honor Lecture

Dr. Steve Nelson, FCCP

#### Distinguished Scientist Honor Lecture

Dr. Robert O. Crapo, FCCP

#### Alfred Soffer Award for Editorial Excellence

Cynthia T. French

#### Alton Ochsner Award Relating Smoking and Health

Dr. Ronald G. Harvey

### Canadian Thoracic Society Christie Memorial Lecture

Dr. Peter Paré

### Canadian Thoracic Society Canadian Institute of Health Research Award

Dr. Francois Maltais

### International Partnering for World Health Award

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### The CHEST Foundation Awards

Two annual CHEST Foundation Awards were presented during Convocation ceremonies:

**The Association of Specialty Professors and The CHEST Foundation Geriatric Development Research Award:** Dr. Renee D. Stapleton

**The Roger C. Bone Advances in End-of-Life Care Award:** Dr. Daniel E. Ray, FCCP

### The CHEST Foundation Humanitarian Awards

The Humanitarian Awards Program provides recognition awards and sustaining grants for nonprofit and nongovernmental health-related organizations benefiting from the expertise and volunteer commitment of ACCP members. This year, The Foundation conferred \$200,000 to the organizations benefit-

ting from the volunteer efforts of 16 ACCP members. View the award winners at [www.chestfoundation.org](http://www.chestfoundation.org).

### The CHEST Foundation Abstract Award Winners

Each year, through its extensive awards program, The CHEST Foundation confers awards to ACCP members in clinical research in chest and critical care medicine. In 2005, The CHEST Foundation proudly awarded over \$600,000 for research, leadership in end-of-life care, and pro bono service. In 2006, The Foundation continued the tradition of recognizing and rewarding health-care professionals who are making a difference in the lives of patients and their families.

The CHEST Foundation 2006 Clinical Research Award Winners and Clinical Research Trainee Award Winners are listed on The CHEST Foundation Web site at [www.chestfoundation.org](http://www.chestfoundation.org).

The following awards were presented on-site at CHEST 2006:

#### Alfred Soffer Research Awards

##### Finalists

Dr. Richard J. Brill (Winner)

Dr. Theodore G. Liou, FCCP (Winner)

Dr. Surya Prakash Bhatt

Dr. David E. Ost, FCCP

Dr. Mark B. Berger, FCCP

Dr. Alpesh Amin

#### Young Investigator Awards

##### Finalists

Dr. Minh Luan N. Doan (Winner)

Dr. Marcin Golec (Winner)

Dr. Jennifer A. Svetleic (Winner)

Dr. Grayson H. Wheatley

Dr. Kala K. Davis

Dr. J. Matthew Brennan

Dr. Steven A. Baroletti

Dr. Daniel R. Ricciuto

Dr. Dee A. Ford

Dr. Tarek A. Dernaika

Dr. Anthony J. Zachria

Dr. Lee M. Arcement, FCCP

Dr. Robert Evangelidis

Dr. Inderpal S. Grover

Dr. Kelly J. Smith

Dr. Brad D. Vincent

Dr. Jeff Reid

Kelly A. Kreuter

Dr. Yochai Adir

Dr. Gautham Ravipati

#### Top Ten Best Poster Awards

##### Finalists

Dr. Timothy A. Morris, FCCP (Winner)

Dr. Jeffrey J. Swigris

Dr. Pyng Lee

Dr. Marilyn G. Foreman, FCCP

CAPT Kevin K. Chung, MC, USA

Dr. Rebecca L. Legg

Dr. Keith M. Rose

Dr. Nina N. Bowman

Dr. Charles Feldman, FCCP

Dr. Babith J. Mankidy

### Case Report Awards (by category)

Airway I: Dr. Heath E. Latham

Airway II: Dr. Marcus P. Kennedy

Airway III: Dr. Steven Kadiev

Bronchology I: Dr. Jason M. Goldbin

Bronchology II: Dr. Perry G. Nystrom

Cardiovascular: Dr. Naricha Chirakalwasan

Critical Care I: Dr. Michelle A. Prichett

Critical Care II: Dr. Anil C. Singh

Cancer Cases II: Dr. Tereza Martinu

Cancer Cases I: Dr. Razaq A. Badamosi

Interstitial Lung Disease: CAPT Jeremy C. Pamplin, MC, USA

Infectious Disease I: Dr. Rajesh V. Babu

Infectious Disease II: Dr. Louis M. D'Avignon

Infectious Disease III: Dr. Nisha Rathi

Pleural Disease I: Dr. Omar S. Hussain

Pleural Disease II: Dr. Jennifer L. McCann

Pulmonary Hypertension: Dr. Paul M. Strachan

Gynecologic and Pediatric Curiosities:

Dr. Jonathan T. Puchalski

Miscellaneous I: Dr. Richard C. Kamm, Jr.

Miscellaneous II: Dr. Faisal Latif

Diffuse Lung Disease: Dr. Won Y. Lee

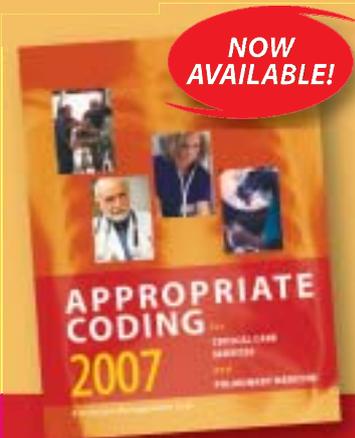
Drug Reactions: Dr. Maen Alqdah

Sleep and Breathing: Dr. Peggy Rahal

The Hole Truth: Dr. Gregory H. Howell

For information on The CHEST Foundation 2007 awards, watch [www.chestfoundation.org](http://www.chestfoundation.org) for updated information.

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### Watch for more CHEST 2006 Wrap-up coming in February!

## We're in the News

The American College of Chest Physicians welcomed substantial media coverage surrounding the scientific abstracts presented at CHEST 2006 in Salt Lake City.

Electronic press kits, promoting more than 60 abstracts, were sent to over 700 media contacts across the United States and Canada. Abstracts generating the most media interest related to the ability of statins to protect smokers from lung damage and how exercise can aid smoking cessation.

Although preliminary results are still being calculated, hundreds of print, broadcast, and Internet stories have appeared thus far in such media outlets as the Associated Press, Reuters, Bloomberg News, *Los Angeles Times*, *Washington Post*, *Newsday*, *New York Daily News*, CNN, MSNBC, FOX National News, CBC News, and over 300 preliminary television broadcast stories in such top markets as New York, Chicago, Los Angeles, Dallas, and Boston.

# CHEST 2006 WRAP-UP



## Honors Bestowed at The CHEST Foundation Dinner

**M**r. Paul Shaffer, Musical Director of the Late Show with David Letterman, was presented with a Special Humanitarian Award at the *Making a Difference Awards Dinner* celebration in Salt Lake City, UT, during CHEST 2006. In a special awards ceremony, Dr. Diane E. Stover, FCCP, immediate past Chair of The CHEST Foundation's Board of Trustees, presented her good friend, Paul Shaffer, with The CHEST Foundation's Special Humanitarian Award.

This award acknowledges the outstanding pro bono service Mr. Shaffer has provided The CHEST Foundation. He has twice donated his time and talent to serve as emcee at the *Making a Difference Awards Dinner*, first in Seattle, WA, in 2004, and again this past year in Salt Lake City, UT. In another display of generosity, Mr. Shaffer lent his talent and celebrity status to The Foundation when he agreed to appear in and narrate The CHEST Foundation's 10th Anniversary Commemorative video, which was debuted at the *Making a Difference Awards Dinner* in Salt Lake City.

In every instance, Mr. Shaffer's involvement has brought about a great deal of joy, excitement, and interest for

The Foundation. The CHEST Foundation is forever grateful to Mr. Shaffer for his generosity and commitment.

The CHEST Foundation also paid tribute to outgoing Chair and longtime member, Diane E. Stover, MD, FCCP.

Mr. Paul Shaffer bestowed to her a gift of thanks and directed everyone's attention to a special video that highlighted Dr. Stover's years of dedication and involvement with The CHEST Foundation.

Dr. Stover has played an integral role in The CHEST Foundation since its creation a decade ago, first by becoming a Board of Trustees member in 1998. She was elected President of the Board of Trustees in 2002 and served for 2 years in that capacity until becoming Chair in 2004. As a leader of The Foundation during its formative years, Dr. Stover's desire to advance The Foundation was communicated through the three themes she put forth: face, focus, and fundraising.

During her tenure, Dr. Stover fostered awareness and growth in the four areas of focus central to The CHEST Foundation. She challenged The Foundation's Development and Marketing Committees to expand the donor base, while ed-

ucating members and strategic partners on the many educational programs and resources available through The CHEST Foundation. She demonstrated her commitment to The Foundation's Clinical Research Awards program by assisting in its expansion through development of strategic partnerships with patient advocacy groups, as well as serving as an annual reviewer for the LUNGEvity Foundation/CHEST Foundation Award in Lung Cancer Research.

Dr. Stover's passion and work to bring about a tobacco-free world was the impetus that provided The Foundation with the tobacco prevention program and many of the antitobacco products that are currently available to ACCP members and their patients. In 1999, Dr. Stover, serving as the Chair of the Task Force on Women & Girls, Tobacco, & Lung Cancer, directed the Task Force in creating the first tobacco prevention speakers' kit, which has just been updat-

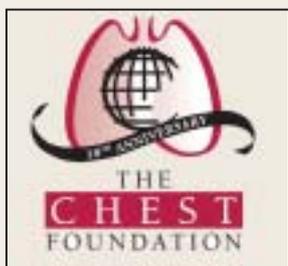


Mr. Paul Shaffer (left) received a Special Humanitarian Award from Dr. Diane Stover and Dr. D. Robert McCaffree at the Making a Difference Awards Dinner.

ed and released as a fourth edition, titled "Make the Choice: Tobacco or Health?" The new speakers' kit has already been distributed to classrooms throughout Illinois. Additionally, the speakers' kits have inspired other ACCP members to translate and adapt them for use in Asia, France, and the Indian subcontinent.

The ACCP and The CHEST Foundation leadership and staff congratulate Dr. Diane Stover on her many contributions to The Foundation and her impressive legacy of leadership.

View The CHEST Foundation's 10th Anniversary Commemorative video at [www.chestfoundation.org](http://www.chestfoundation.org).



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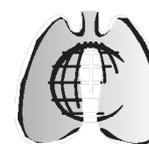
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# Second Dopamine Agonist Approved for Restless Legs

BY ELIZABETH MECHCATIE  
Elsevier Global Medical News

While misdiagnosis of restless legs syndrome remains common, the Food and Drug Administration has increased the agents available to treat this movement disorder by approving the dopamine agonist pramipexole for moderate to severe cases.

Pramipexole is the second drug and the second dopamine agonist to be approved for this condition. The first was ropinirole (Requip), another dopamine agonist approved last year for restless legs syndrome (RLS), which affects as many as 3% of the population. Dopamine agonists had been considered first-line treatments for moderate to severe RLS by expert consensus panels before they were approved, according to Dr. John Winkelman, medical director of the Sleep Health Center at Brigham and Women's Hospital, and Harvard Medical School, Boston.

While it will take more time for recognition of RLS to improve, "the good news is that the treatments are so effective and generally so well tolerated, it is gratifying to treat," and response to treatment is typically rapid, Dr. Winkelman said. It is "the unusual patient who doesn't have some response to

one of the dopamine agonists," he added.

Both pramipexole, marketed as Mirapex by Boehringer Ingelheim, and ropinirole, marketed as Requip, have been available for almost 10 years, since they were approved for Parkinson's disease. Dr. Winkelman is a consultant to Boehringer Ingelheim and to ropinirole manufacturer GlaxoSmith-Kline, as well as other companies that manufacture products for insomnia and other sleep disorders.

Pramipexole was significantly more effective than placebo in four randomized, double-blind, 3- to 12-week studies of about 1,000 patients with moderate to severe RLS, which evaluated the effect of treatment on a scale based on patient-reported symptoms and a Clinical Global Impressions scale.

Dr. Winkelman was the lead author of one study of 344 patients, published in September, which found that at 12 weeks, those on three fixed doses of pramipexole improved significantly more from baseline than those on placebo in a scale that represented patient rating of symptom

severity, which covers effects on sleep and next-day functioning. In addition, 70%-75% of patients on the three doses of pramipexole studied were rated as "very much improved" or "much improved" on a clinician rating scale, compared with 51% of those on placebo, a significant difference (Neurology 2006;67:1034-9). A

strong placebo effect was seen on both of these primary end points, which he noted was true for disorders where people are asked how they are doing.

Side effects were generally mild, with no serious adverse

events. Nausea was the main side effect that was more common in patients on the drug (19% vs. almost 5%), but was mild and transient. Because this was a forced titration study, where patients are titrated up to the preassigned dose, even if they responded to a lower dose, side effects may have been more common than if doses were individualized, he said.

Interestingly, a benefit of the low dose of 0.125 mg over placebo was seen at 1 week, he pointed out.

RLS becomes more prevalent as people age, with the typical age of onset in the 40s

and 50s. The symptoms and effects of the disorder are not well recognized, he said, noting that RLS interferes with a person's daytime functioning and ability to fall asleep and stay asleep. People with moderate to severe RLS have symptoms at least three times a week.

The indications section of the revised label for pramipexole lists diagnostic criteria for RLS, including an urge to move the legs that is "usually accompanied or caused by uncomfortable and unpleasant leg sensations," symptoms that begin or worsen during periods of inactivity, such as lying or sitting; and symptoms that are partially or totally relieved by movement such as walking or stretching.

Why a dopamine agonist works in restless legs syndrome is not entirely clear, he said. Dopamine is potentially involved in sensorimotor integration, and RLS is considered a sensorimotor disorder.

The dopamine agonist doses used for RLS are much lower than doses used to treat Parkinson's. The FDA-recommended starting dose is 0.125 mg taken once daily 2-3 hours before bedtime. If necessary, the dose can be increased every 4-7 days to 0.25 mg daily and, if necessary, to 0.5 mg daily after another 4-7 days. The revised label says that there is no evidence that a 0.75 mg daily dose provides any more benefit than the 0.5 mg dose. ■

**'THE GOOD NEWS IS THAT THE TREATMENTS ARE SO EFFECTIVE AND GENERALLY SO WELL TOLERATED, IT IS GRATIFYING TO TREAT.'**

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## Mayo Clinic Study: Evaluate Sleep Apnea As Part of Preventive Cardiology

CHICAGO — Obstructive sleep apnea is associated with subclinical coronary artery disease independent of the traditional cardiovascular risk factors, Dr. Dan Sorajja reported at the annual scientific sessions of the American Heart Association.

Moreover, the severity of subclinical coronary artery disease as reflected by the extent of coronary artery calcium (CAC) on electron beam CT increases with obstructive sleep apnea severity. For this reason, the presence and severity of obstructive sleep apnea ought to be incorporated into coronary artery disease risk stratification and preventive cardiology efforts, according to Dr. Sorajja of the Mayo Clinic, Rochester, Minn.

He reported on 202 consecutive patients with no history of coronary artery disease who underwent electron beam CT within 3 years of polysomnography at the Mayo Clinic. They were a median of 50 years old, with a mean body mass index of 33 kg/m<sup>2</sup>. More than half were dyslipidemic and 44% had hypertension.

CAC was present in 67% of patients with and in 31% without obstructive sleep apnea. And apnea, in turn, was present in 76% of those with CAC. The mean CAC score was 144 Agatston units in those with obstructive sleep apnea and 26 Agatston units in those without.

In a multivariate analysis, the adjusted odds ratio for CAC increased in stepwise fashion with each increasing quartile of obstructive sleep apnea severity as determined by the apnea-hypopnea index (AHI). The prevalence of coronary artery disease was 2.1-fold greater in patients in the

second obstructive sleep apnea severity quartile, with an AHI of 5-13, than in those in the lowest quartile. The CAC prevalence was 2.4-fold greater among patients in the third quartile, with an AHI of 14-32, than in the first. And in individuals in the top quartile, where the mean AHI was 63, the prevalence of CAC was 3.3-fold greater than in the first quartile.

The chief limitation of a cross-sectional study such as this one is the potential for selection bias, he conceded.

Obstructive sleep apnea is a common medical condition. The prevalence of significant obstructive sleep apnea symptoms has been estimated at 4%-9% among middle-aged adults. The condition has previously been shown to be a cause of hypertension. It is also associated with an increased risk of MI and with elevated rates of several important risk factors for coronary artery disease, including dyslipidemia, diabetes, and obesity, Dr. Sorajja noted.

—Bruce Jancin

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# Health Plan Feedback to Doctors Improved Asthma Care

BY JANE SALODOF MACNEIL  
Elsevier Global Medical News

SAN FRANCISCO — What health plans tell physicians can make a difference in the quality of care given to poor children with asthma, according to a study of about 4,500 children covered by 18 Medicaid managed care plans in Tennessee and Washington state.

Two types of communication significantly increased the proportion of children with severe asthma who filled their controller prescriptions, Dr. William O. Cooper reported at the annual meeting of the Pediatric Academic Societies.

The first was feedback about how the provider compared to other physicians



**Children in plans with feedback filled their controllers 17.6 days more on average.**  
**DR. COOPER**

with respect to quality-of-care benchmarks. The other was provider notification of an asthma-related hospitalization or an asthma-related emergency room visit by a child in the physician's panel of patients.

"I think there are things that health plans do in the way they interface with providers that could potentially improve

coverage for their children," Dr. Cooper of Vanderbilt University said in an interview at the meeting, which was sponsored by the American Pediatric Society, Society for Pediatric Research, Ambulatory Pediatric Association, and American Academy of Pediatrics.

The retrospective cohort study reviewed records from 2000 to 2002 for 3,058 children in Tennessee and for 1,440 children in Washington state.

The children, who ranged in age from 2 to 17 years, had moderate to severe asthma. They were covered by 11 health plans in Tennessee and 7 plans in Washington state.

Investigator interviews with the plans' medical directors determined that nine plans in Tennessee and five in Washington state provided feedback on quality of care to providers.

A smaller number of plans, seven in Tennessee and three in Washington state, provided notification.

As an example of feedback, Dr. Cooper offered the following paraphrase of an insurer telling a physician, "In our health plan, 70% of children [with asthma] have controller medications. We looked at your panel of patients and only 30% [do]. Here's how you are doing compared to the other providers."

All told, 1,413 children were in plans that provided neither feedback nor notification, 1,341 were in plans that provided only feedback, 215 were in plans that provided only notification, and 1,529 were in plans that provided feedback and notification.

The study looked at the filling of prescriptions for asthma controllers (inhaled corticosteroids, cromolyn, or leukotriene

modifiers) during a 365-day follow-up period.

Dr. Cooper and his coinvestigators at Vanderbilt and the University of Washington reported that children in plans with both components filled their controllers 17.6 days more on average than children in plans with no feedback.

If the plans had one component, either notification or feedback, then the benefit averaged 10.3 more days of filled controllers.

Notification, by itself, resulted in more

than 200 days that controllers were filled on average, the most of any option for the population as a whole.

The effects of feedback and notification were most pronounced for children with more severe asthma, as defined by the filling of three or more beta-agonist prescriptions in the 6 months prior to their entering the study.

In this population, only 77.4% of children filled their controllers if their health plans did not provide feedback or notification. The proportion increased to 81.6%

with notification and 82.1% with feedback to physicians. When feedback and notification were both used, 85.5% filled their controllers (odds ratio 1.7, compared with children in plans that provided neither form of communication).

The mean number of days that controllers were filled also increased from 144 with no communication to 181 with feedback to 327 with notification. On average, children in plans with feedback and notification filled their controllers for 225 days.



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

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

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

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

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

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

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

**ADVERSE REACTIONS: Clinical Trials:** In clinical trials using multiple doses of cefepime, 4137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g IV q12h). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse events was very similar at daily doses of 500 mg, 1 g, and 2 g q12h (0.8%, 1.1%, and 2.0%, respectively). However, the incidence of discontinuation due to rash increased with the higher 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 overdose has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability. (See **PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the complete prescribing information.)

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# knock, knock.



Gram-positive infection?

**WE'RE THERE, TOO.\***



\*For gram-positive infections due to susceptible strains of indicated organisms in treating moderate-to-severe pneumonia or febrile neutropenia.

MAXIPIME is contraindicated in patients who have shown an immediate hypersensitivity reaction to MAXIPIME, cephalosporins, penicillins, or any other  $\beta$ -lactam antibiotics.

In North American clinical trials of MAXIPIME at a dose of 0.5 to 2 g IV q12h, the most common adverse events were local reactions (3%), including phlebitis (1.3%), pain and/or inflammation (0.6%); rash (1.1%). 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 administration of antibacterial agents.

HCAP defined as: healthcare-associated pneumonia.

Please see brief summary of prescribing information on adjacent page.



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