To Err Is All Too Human With Powder Inhalers

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — Nearly one-third of patients with asthma or chronic obstructive pulmonary disease incorrectly used their dry powder inhalers in a study of 224 patients reported at the annual meeting of the American College of Chest Physicians.

The error rate increased with age, severity of airway obstruction, and lack of prior training, reported Dr. Siegfried Wieshammer of the Ortenau Hospital Offenbach, Germany, and Jens Dreyer of the University of Heidelberg, Mannheim, Germany.

Dry powder inhalers, generally marketed as being easy to use, were developed in recent years to coordinate actuation of the device with inspiration.

"We conclude that many health care professionals do know how to instruct their patients in inhaler use, but this is not done to the necessary extent," Dr. Wieshammer said. "The current proliferation of inhaler types may become detrimental to the quality of care, because busy doctors don't have sufficient time to become adequately familiar with the strengths, weaknesses, and pitfalls of all these new developments.

"Doctors should limit their selection to a small number of inhaler types [that have] operating principles they can study in detail.

Patients younger than 60 years had a 20% error rate using dry powder inhalers, versus 42% among those 60 years or older.

Neuropsychiatric events fuel revisions.

FDA Panel Backs Label Changes for Antiviral Flu Drugs

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

GAITHERSBURG, MD. — Prompted by concerns about an association between antiviral drugs and neuropsychiatric events in patients with influenza, a closely divided Food and Drug Administration advisory panel voted on Nov. 27 to recommend revised labeling for oseltamivir and zanamivir.

The events have been reported in Japanese children predominately and include fatalities related to self-injurious behavior. In an 8 to 6 vote on oseltamivir, the FDA's Pediatric Advisory Committee called for a statement making clear that the neuropsychiatric events have been rare, and that they also have been described in patients with influenza who are not on antiviral treatment. The panel's suggested oseltamivir labeling would state that the contribution of the drug in these cases remains unclear. Some panelists said that the abrupt nature of the onset of these events also should be described.

Oseltamivir, marketed as Tamiflu by Hoffmann-La Roche Inc., is an oral neuraminidase inhibitor approved for the treatment and postexposure prophylaxis of influenza in adults and children older than 1 year.

The current label's precautions section includes a statement about postmarketing reports, mostly in Japan, "of self-injury and delirium" associated with oseltamivir in patients with influenza, primarily among pediatric patients. That statement, added in November 2006, says that, "the relative contribution of the drug to these events is not known," and recommends that patients with influenza "should be closely monitored for signs of abnormal behavior throughout the treatment period.

Whether the neuropsychiatric events should be described.

Lung Transplantation Value Questioned in CF

BY MARY ANN MOON
Elsevier Global Medical News

Lung transplantation does not improve survival in most children who have cystic fibrosis, suggest data published in the New England Journal of Medicine.

In a study estimating the surgery's survival benefit in 514 children who had CF and who were put on a waiting list for lung transplantation in the United States between 1992 and 2002, the procedure clearly prolonged life expectancy in only five patients—less than 1%, study investigators Dr. Theodore G. Liou of the University of Utah, Salt Lake City, and his associates wrote (N. Engl. J. Med. 2007;357:2186-8).

"Patients with cystic fibrosis and their parents need to be informed that although transplantation may improve quality of life, it may not improve survival. This information is profound implications, Dr. Julian Allen of the Children's Hospital of Philadelphia and Dr. Gary Viner of Children's Hospital, Boston, wrote in an editorial comment accompanying the report.

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events are related to the drug or influenza, it would be useful to include information that reflected ‘our ongoing uncertainty’ and concern about the association, said panelist Dr. Michael Fanit of the division of neonatal-perinatal medicine at the University of Texas at Houston.

The public should be made aware that the reported adverse reactions that were infrequent, came on abruptly, and were transient—but occasionally resulted in fatalities, he said. Dr. Fant highlighted one report that he found particularly alarming, in which a 14-year-old Japanese boy taking an antiviral woke up and found himself hanging from a third-floor window with his feet on a 10-cm ledge.

The panel recommended that similar information be added to the label for the other available neuraminidase inhibitor, zanamivir, to reflect a similar but fewer reports associated with this drug. The current label for zanamivir, marketed as Relenza by GlaxoSmithKline, lists seizures and syncope as CNS reactions associated with its use.

Neuropsychiatric events also have been reported in patients taking two older antiviral drugs for the treatment and prophylaxis of influenza: amantadine and rimantadine. Although the panel reviewed these two drugs at the meeting, too, the members unanimously agreed that the information on CNS reactions in the labels of these two M2 inhibitors was adequate.

The label for amantadine includes a warning about suicide attempts, personal- ity changes, aggressive behavior, and other CNS reactions in people using the drug. The rimantadine label includes a precaution about ataxia, agitation, and other CNS reactions in clinical trials of the drug.

The FDA usually follows the advice of its advisory panels, which is not binding. This was the third time since 2007 that the FDA’s Pediatric Advisory Committee has met to discuss neuropsychiatric events associated with oseltamivir. A pediatric safety review in 2005 found neuropsychiatric events associated with the drug, mostly in Japan, as well as 12 deaths in Japanese pediatric patients.

By the second meeting, in November 2006, more cases had been identified, still predominantly in Japan, where antivirals are used widely for treating influenza. Most reports fell into the category of delirium with prominent be- havioral disturbances, with symptoms typically occurring after one to two doses. As of November 2006, 18 deaths in people aged 17 years or younger had been reported, including 3 children activated and managed.

Regarding influenza-specific error rates, Amantadine had the lowest error rate (4.9% of 22 visits), followed by Discus (27% of 86 visits), Turbuhaler (35% of 109 visits), and HandiHaler (53% of 32 visits), Dr. Wieshammer said.

The error rate increased significantly with age. Patients aged younger than 60 years had a 20% error rate, whereas those aged 60 years or older had an error rate of 42%. The error rate also increased with the severity of airway obstruction. Dr. Wieshammer speculated that cognitive deficits occurring with the aging process, as well as a COPD-specific cognitive de- terioration, make it difficult for older pa- tients with advanced COPD to properly use their inhaler.

Instruction by medical personal on how to use the inhaler had a major effect on the error rate. Only 23% of trained patients made essential errors, compared with 52% of those who received no in- struction, a statistically significant differ- ence. This was somewhat surprising, as a lack of inhaler skills among health care professionals has been repeatedly described, Dr. Wieshammer said.

Using a risk-prediction model, the probability of inhaler misuse was only 9% in the favorable case of an 18-year-old patient with normal lung function and previous instruction who was being treated with Turbuhaler. At the other end of the scale, the probability of inef- fective inhalation was 83% in an 80-year- old with moderate to severe obstruction and no prior instruction.

Dr. Wieshammer did not advise against the use of dry powder inhalers in the elderly, but advocated that older pa- tients with advanced COPD should be asked to demonstrate their inhalation technique at every health care encounter. If handling errors can’t be eliminated by follow-up training, then a metered-dose inhaler, in combination with a large-vol- ume spacer, might be a valuable treat- ment alternative in a substantial proportion of these patients, he said.

Dr. Wieshammer disclosed that he has received funds from Astrazeneca Pharmaceu- ticals LP and GlaxoSmithKline Inc. for arranging educational courses and for speaking engagements in the last 12 months. Dr. Dreyhaupt reported that he has nothing to disclose.

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Prophylactic Steroids Helped 9/11 First Responders

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — Prophylactic inhaled corticosteroids appear to have prevented or reduced lung injury among first responders at the World Trade Center, according to the first study of its kind.

Budesonide taken via Turbuhaler twice daily for 4 weeks beginning 1 week after the attacks of Sept. 11, 2001, reduced respiratory symptoms and improved pulmonary function and quality of life among 158 New York City firefighters, Dr. David Prezant, FCCP, and associates reported in a poster at the annual meeting of the American College of Chest Physicians.

Dr. Prezant called the findings hypothesis generating, although they raise the issue of whether patients exposed to smoke and soot laden air from the recent California wildfires should be similarly treated.

At 2 years after the 9/11 attacks, treated firefighters had significantly higher vital capacity than controls.

"Disasters will occur in the future, and we would like to establish the framework for things to come," Dr. Prezant said.

The steroids were offered free of charge, courtesy of AstraZeneca Pharmaceuticals LP, to about 11,000 firefighters, but only 2,708 agreed to enroll, and just 158 (6%) completed 4 weeks of treatment.

The most common reasons cited for not enrolling were confusion of corticosteroids with anabolic steroids, and fear of side effects such as osteoporosis.

A common reason for not completing treatment was lack of immediate benefit. Firefighters were told orally and in writing not to expect an immediate effect, but they often used the drug for only 2-3 days, suggesting that a continuous education process is needed, Dr. Prezant said.

While respiratory protection is the primary means of preventing lung injury, first responders often shun it during the stress of an emergency situation, Dr. Prezant noted.

"To be fair, not everyone would use prophylaxis," he said.
Adenovirus 14 Tied to Cluster of Hospitalizations

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — During the winter of 2006 and the spring of 2007, adenovirus 14 caused a community outbreak of respiratory disease in Oregon, with a fatality rate of 19%. Dr. Paul Lewis reported at the annual meeting of the Infectious Diseases Society of America.

“This seemed to come out of nowhere,” Dr. Lewis, a public health physician with the state of Oregon and a pediatric infectious disease physician with Oregon Health and Science University, Portland, said of the outbreak. “In patients with serious respiratory illness without an identified etiology, clinicians should think about viruses.”

The cluster was first identified in the spring of 2007 by his associate, Dr. David Gilbert, who was making rounds in the intensive care unit at Providence Portland Medical Center and thought it was odd that 4 of 13 patients had adenovirus infections, which are typically mild and self-limited.

“When we called other hospitals in the Portland area, we almost fell out of our chairs because they all had seen recent severe and fatal cases of adenovirus,” said Dr. Lewis.

The investigators assessed a cohort of 678 adult patients, which was published in Archives of Internal Medicine, found that being African American was associated with a hazard ratio of 1.73 for visits to the emergency department and 2.01 for hospitalizations after controlling for potential confounders.

No significant differences between groups were reported in use of asthma controller medication in the previous 2 weeks. However, African Americans reported using short-acting β-agonists more than twice as often as did white patients in the previous 3 months (odds ratio 2.22), and their use of other rescue medications was also higher, Dr. Sara E. Erickson of the University of California, San Francisco, and her colleagues wrote.

Asthma monitoring was more prevalent among African Americans, although both whites and blacks had a similar level of exposure to asthma education and similar rates of having seen an asthma specialist in the prior year.

These findings had no clear explanation, the authors said, and the cause of the disparity is likely complex. They acknowledged that their findings might have been confounded by unmeasured socioeconomic factors or comorbid diseases, for which data were not collected. They also suggested that physicians might encourage black patients more often than white patients to seek treatment in the emergency department for their asthma exacerbations or that cultural beliefs about asthma might play a role. Reporting bias was another possibility.

“Lobar consolidation was the most common pattern,” Dr. Lewis reported that 22 (71%) of the adenovirus 14 patients required hospitalization, and 6 (19%) died. Of the hospitalized patients, 16 (73%) required ICU care, 13 (59%) required mechanical ventilation, and 8 (36%) required blood pressure support with vasopressors.

“Infusion control was a great concern to hospitals that saw multiple cases,” Dr. Lewis said. “Many patients were isolated with severe acute respiratory syndrome-like precautions.” There was a health care worker at an ICU taking care of one of these patients who was subsequently admitted to that ICU with adenovirus 14,” he added. “That’s our only known possible case of transmission, but we cannot be sure it was not acquired in the community.”

Treatment included “lots of empiric antibiotics.” Cidofovir was used in six patients, two of whom died.

A survey of 541 athletic trainers affiliated with National Collegiate Athletic Association sports programs found that only 20% had a specific, written plan for managing asthma exacerbations during practices or games, Dr. Jonathan Parsons and colleagues reported at the annual meeting of the American College of Chest Physicians.

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Written asthma treatment protocols are recommended by the National Athletic Trainers’ Association and by the National Asthma Education and Prevention Program, administered by the National Heart, Lung, and Blood Institute.

In all, 61% of responders said their program mandates that albuterol or short-acting β-agonist inhalers be present at all practices, and 59% said such treatment was available at all games.

Because it is not possible to determine when an athlete may have an asthma attack or how severe it may be, having a plan and necessary medication available is essential to improve outcomes, Dr. Parsons, associate director of the Ohio State University asthma center, Columbus, told reporters at a press briefing. He cited a study that identified 61 athletes with asthma who died during or after a sporting event from 1993 to 2000—most of whom were younger than 21 years of age (81%) and had a known history of asthma (91%) (J. Allergy Clin. Immunol. 2004;113:264-7). Just 17% of NCAA respondents indicated that objective testing is performed when an athlete presents with shortness of breath during exercise. “This likely results in missed diagnoses and inaccurate diagnoses, which exposes athletes to unnecessary medication and unnecessary health morbidity,” Dr. Parsons said.

Dr. Parsons and his colleagues recently reported that exercise-induced bronchospasm is relatively common among varsity athletes (39% of 107 athletes), and that symptoms were not predictive of such bronchospasms (Med. Sci. Sports Exerc. 2007;39:1487-92).

A minority of programs (22%) had a pulmonologist as an active or formal member of their sports medicine program. However, when they did, the impact was significant.

Programs with pulmonologists were 2.6 times more likely to have a written protocol for asthma management, 1.6 times more likely to have inhalers available during all practices, and 1.7 times more likely to have inhalers available during all games, differences that were all statistically significant.
Study Supports Endobronchial Valves for Emphysema

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — The Zephyr endobronchial valve significantly improved lung function and exercise capacity in patients with severe emphysema in the first prospective, randomized, multicenter trial to evaluate endobronchial valves.

The device offers patients a minimally invasive and potentially reversible method of lung-volume reduction without the potential risk of significant morbidity associated with open surgical reduction. The unidirectional silicone valve, inserted via fiberoptic bronchoscopy, is designed to block inhaled air from entering diseased portions of the lung while permitting air and fluids to escape during exhalation. The device is limited to investigational use in the United States, but has been sold on a limited basis in Europe and the Asia-Pacific regions.

Results of the VENT (Endobronchial Valve for Emphysema Palliation Trial) indicate that the procedure has an acceptable safety profile, and is particularly effective in patients with complete fissures, effective lobar exclusion, and left-sided disease.

“Most important—and what we are very interested in—is that there was a greater magnitude of effect in prespecified subsets of patients, particularly with respect to technical efficacy and physiologic potential,” VENT investigator Dr. Frank C. Sciurba, director of the emphysema research center at the University of Pittsburgh, said at the annual meeting of the American College of Chest Physicians.

Dr. Sciurba was one of five investigators to present data from VENT. The study was conducted at 31 sites from December 2004 to April 2006, and included 321 patients (aged 40-75 years) with severe heterogeneous emphysema, predominantly affecting the upper lobes.

In all, 220 patients were randomized to implantation with Zephyr endobronchial valves (manufactured by Emphasys Medical Inc.) and 101 patients to medical management, defined as maximal medical treatment for stable chronic obstructive pulmonary disease as recommended in the 2001 GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines. Typically, three to four valves were implanted per lobe under moderate sedation. All patients were required to undergo pulmonary rehabilitation before and after surgery.

The study met its coprimary efficacy end points of mean percent change in forced expiratory volume in 1 second (FEV1) and 6-minute walk test at 6 months. FEV1 improved by 5.8% in the intervention group, and fell by 0.6% in the control group. The 6-minute walk scores improved by 1.7% in the intervention group, and fell by 4% in the control group. The differences in these outcomes were significant, but were of modest magnitude, said Dr. Sciurba.

He reported that his center received funding to conduct the trial from Emphasys, which sponsored the study.

A 15% improvement in FEV1, (a predefined measure of a clinically meaningful difference) was achieved by 26.4% of patients in the intervention group, compared with 16% in the control group. Similar increases were observed for 6-minute walk scores (27% vs. 20%).

Secondary end points of quality of life—as measured by the St. George’s Respiratory Questionnaire, Modified Medical Research Council Dyspnea Scale scores, and exercise capacity as measured by incremental cycle ergometry—were significantly improved in the intervention group.

Major complications occurred in 6% of patients in the intervention group and in 1% of controls. The difference did not reach statistical significance. Distal pneumonia, which had been a strong theoretical concern before the study, was increased at 6 months in the treatment group, but there was no difference between groups at 12 months, Dr. Sciurba said.

There were eight deaths in the study. One, a massive hemoptysis, was considered procedure related, he said.

Valve expectoration or migration occurred in 6.4% of patients. Valve removal was attempted in 31 patients (14%), primarily because of a lack of efficacy, and was successful in 85 of 87 attempts (98%).

Dr. Sciurba said he was comforted by the fact that the procedure is reversible should patients not achieve the desired results. But he added that, based on analogies from lung-volume reduction surgery, bilateral procedures should result in significantly greater impact than unilateral procedures.

“We believe this procedure is one of several emerging technologies that may eventually prove beneficial to our patients,” Dr. Sciurba said in an interview. “My hope is that other minimally invasive technologies will be proved to complement these valves and become part of a tool chest for the interventional bronchoscopist to improve lung function and symptoms.”

In October 2007, the Food and Drug Administration granted expedited review for a premarket approval application, submitted by Emphasys, requesting approval to market the Zephyr valve in the U.S.
Survival Benefit Uncertain

Lung Transplant • from page 1

reported a survival benefit, but another by Dr. Liou and his associates showed no survival benefit. This discrepancy generated “heated controversy,” the editorialists wrote.

To address these discrepant findings, Dr. Liou’s group conducted a new study using data from the Cystic Fibrosis Patient Registry and from the Organ Procurement and Transplantation Network, which allowed assessment of nearly four times as many patients as were previously studied.

This larger data set afforded the new study greater statistical power. The investigators identified 514 children with a wide range of lung function and prognoses who were on the waiting list for lung transplantation from 1992 through 2002, which represented “essentially the entire U.S. experience with lung transplantation for CF” during that period.

A total of 248 underwent transplantation, 120 of whom died after the procedure (median survival 1,037 days). Of the 266 children who did not receive transplants, 141 died.

The researchers performed statistical modeling that accounted for the effects of multiple covariates (Burkholderia cepacia infection, age, diabetes status, Staphylococcus aureus infection) before and after the procedure to estimate how the surgery would alter each patient’s risk of death.

A total of 509 children “did not derive a significant estimated survival benefit.” Moreover, most patients (315) “were at significant risk for harm” from the surgery.

“Actuarial survival for lung transplantation for CF has not appreciably changed in the past several years; thus the ability of our model to predict survival outcomes for patients undergoing transplantation after 2002 is likely to be high,” the investigators said (N. Engl. J. Med. 2007;357:2143-52).

“We cannot comment on the effect of lung transplantation on the quality of life for children with CF that is so severe that they are considered for this procedure,” they noted. “The results underscore that sustained, multidisciplinary care rather than lung transplantation is central to longevity in children with CF.”

Dr. Stephen Rowe, FCCP, comments: In the most definitive retrospective analysis to date, including the pediatric U.S. lung transplant experience from 1992 to 2002, Liou et al. report no significant benefit of the procedure compared to patients listed but not undergoing transplant.

Using a proportional hazards model that included a number of covariates, the authors predicted only 5 of 514 subjects to have derived life-preserving benefit by lung transplant, while 315 had a significant risk of harm. The complexities of appropriate referral for lung transplant are difficult to capture (including quality of life, anticipated time to transplant due to unpredictable waiting lists, etc.), but these data suggest a cautious approach to lung transplant is needed, and frank discussion with families regarding the limited expectation of improved survival.

Perhaps better methods of prioritizing lung transplant recipients will allow allocation of organs to those most likely to attain a survival benefit, particularly until a definitive randomized, controlled trial confirms these findings. Clearly, the best approach to the care of the CF patient is a comprehensive model that maximizes longevity and quality of life while avoiding the need for transplantation as long as possible.
Study Casts Doubt on Post-Trauma Transfusion Protocol

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS — Early transfusion of fresh frozen plasma in the resuscitation of patients with early postinjury coagulopathy appears to be independently associated with an increased risk of subsequent multiorgan failure, according to a prospective cohort study of critically injured patients.

Moreover, the increasingly popular practice of delivering units of fresh frozen plasma (FFP) and packed red blood cells (RBC) in a fixed 1:1 ratio also may be counterproductive in patients with early postinjury coagulopathy and shock. This strategy needs to be reexamined, according to Dr. Jeffrey L. Johnson, director of the surgical ICU at Denver Health Medical Center.

He presented his study of the relationship between transfusion and postinjury multiorgan failure (MOF) at the annual meeting of the Western Surgical Association. The study involved 1,415 Denver Health ICU patients who had survived more than 48 hours after they sustained critical injuries during 1992-2004.

Their mean age was 37 years, and all were older than age 15. Blunt trauma was the mechanism of injury in three-quarters of cases. The mean Injury Severity Score was 30. Twenty-four percent of patients developed MOF. Overall 30-day mortality in the study population was 8%.

In an earlier influential 1997 study, the Denver Health group demonstrated a linear relationship between the number of units of red blood cells delivered within the first 12 hours after injury and the risk of subsequent MOF. Those who got more than 20 units had an MOF incidence in excess of 50%. Multiple organ failure is the leading cause of death in the ICU among critically injured trauma patients.

Dr. Johnson’s study prompted several audience members to vow that they would examine the impact of early use of FFP in a 1:1 ratio with RBC on their own institutional MOF rates.

These new findings underscore how little is understood about the early biology of trauma, according to Dr. Johnson.

“Despite the long recognition of this problem, the role of FFP in the treatment of early traumatic coagulopathy remains poorly understood. We do not know what dose to give; we do not know the best timing of FFP delivery; and we do not fully understand the biology, the safety, or the efficacy of plasma in the setting of early coagulopathy,” he continued.

Dr. Johnson’s study prompted several audience members to vow that they would examine the impact of early use of FFP in a 1:1 ratio with RBC on their own institutional MOF rates.
The Food and Drug Administration approved major changes to the labels of erythropoiesis-stimulating agents (ESAs), addressing serious risks that have been associated with these drugs in patients with cancer or chronic renal failure.

The FDA announced Nov. 8 that it okayed revisions to the boxed warnings and other safety-related changes in the labels of the erythropoiesis-stimulating agents (ESAs). The changes are being made “to make clear recommendations about the safe and effective use of these products and to strengthen the information about the risks that these drugs pose to patients with cancer and to patients with chronic kidney failure,” Dr. Richard Pazdur, director of the FDA’s division of oncology drug products, said during a press briefing.

ESAs have been associated with an increased risk of tumor progression and lower survival rates when used to treat patients with certain cancers, and an increased risk of serious cardiovascular events in patients with chronic kidney failure. Three ESAs are approved for use in the United States: two epoetin alfa products, marketed as Epogen and Procrit, and darbepoetin alfa, marketed as Aranesp. All three are approved for treating anemia in patients with chronic kidney failure and for treating anemia caused by chemotherapy in certain patients with cancer. Epoep and Procrit also are approved for use during or shortly after surgery to reduce the need for blood transfusions in patients undergoing major surgery and for treating anemia caused by zidovudine (AZT) treatment in patients with HIV.

This is the fifth time since Procrit and Epoep were approved in 1989 that the ESA labels have been changed to incorporate safety information. The latest changes incorporate recommendations made this year at a meeting of the FDA’s oncologic drugs advisory committee in May 2007 and a joint meeting of the FDA’s Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in September 2007.

The boxed warning for patients with kidney failure treated with ESAs applies to those on dialysis and those not on dialysis. The label now states that the risk of death and serious cardiovascular events, including myocardial infarction, stroke, and heart failure, is greater when ESAs are administered to achieve higher versus lower hemoglobin levels. The warning cites two clinical trials: one study that compared dosing with hemoglobin targets of 13.5 g/dL and 12.5 g/dL, and a second comparing dosing with target levels of 14 g/dL and 12 g/dL. A separate boxed warning says that dosing in chronic renal failure patients should be individualized to achieve and maintain hemoglobin levels within the range of 10-12 g/dL. “Maintaining higher hemoglobin levels in patients with chronic kidney failure increases the risk for death and for serious cardiovascular reactions,” according to the FDA.

In an important change, the label’s dosing and administration section contains specific recommendations for dosing adjustments and hemoglobin monitoring in patients with chronic renal failure who do not respond to ESAs with adequate increases in their hemoglobin levels. In trials, these patients—hyporesponders—appeared to be at greater risk of serious cardiovascular events than were patients with adequate responses.

The label now says that ESA dosages should not be increased in patients who fail to achieve or maintain a hemoglobin level of 10-12 g/dL after 12 weeks of treatment. Treatment should be discontinued in patients who do not achieve hemoglobin levels sufficient to avoid the need for transfusions. For the ESAs’ cancer indication, the boxed warning now includes a list of cancers—including advanced breast, head and neck, lymphoid, and non-small cell lung cancer—in which ESA dosing to achieve a hemoglobin target level of 12 g/dL or more resulted in a reduced survival time or tumor progression. The warning also states that the risk of shortened survival and increased progression “has not been excluded” in patients on chemotherapy when the target level is less than 12 g/dL. The revised label also emphasizes that ESAs should be used only to treat anemia that patients experience while undergoing myelosuppressive chemotherapy—but not to treat other causes of anemia in people with cancer. In addition, ESAs should be stopped once the chemotherapy course is completed. “These risks should be weighed against the potential for red blood cell transfusions and their associated risks,” Dr. Pazdur said.

Quality of life claims also have undergone significant change. The revised label emphasizes that there are no controlled clinical trial data demonstrating that ESAs improve symptoms of anemia, quality of life, fatigue, or patient well-being in patients with cancer, or in patients with HIV on AZT.

For chronic kidney failure patients, the label has been updated to include data on improvements in exercise tolerance and functional ability that have been associated with ESA treatment. But parts of the section on clinical outcomes such as happiness and well-being have been deleted.

FDA officials emphasized that none of the ESAs is approved for treating fatigue or other symptoms of anemia. In cancer patients, ESAs are not approved for treating anemia associated with other cancer-related causes.

It is clear that the achieved hemoglobin value has a definite impact on cardiovascular outcomes in renal failure patients, said Dr. John Jenkins, director of the FDA’s Office of New Drugs. But in cancer patients, it is less clear whether the ESA dose or the achieved hemoglobin level affects survival and tumor progression.

The FDA is working with Amgen to develop a medication guide for patients, which will explain the risks and benefits of ESA treatment. The agency also will work with Amgen on clinical trials of ESA dosing regimens in different types of cancers to learn more about the potential for tumor progression.
Anti-MRSA Program Succeeds Across Institutions

BY BRUCE K. DIXON
Elsevier Global Medical News

CHICAGO — Multisite implementation of a generic hand-hygiene culture-change program can significantly reduce infections caused by methicillin-resistant Staphylococcus aureus, according to Dr. M. Lindsay Grayson.

In a landmark study involving six urban and rural Australian hospitals, a centrally organized program encouraging the widespread use of alcohol-based hand rubs halved MRSA bacteremia rates, Dr. Grayson told the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

It is the first large multisite study to demonstrate the benefits of a hand-hygiene culture change, said Dr. Grayson, director of infectious diseases at Austin Health, a provider of tertiary health services in Melbourne, and professorial fellow at the University of Melbourne. In fact, it was a single-institution study at Austin Hospital that set the stage for this expanded study (Med. J. Aust. 2005;183:509-14).

“[In the current study, we] introduced alcohol-based hand rubs and alcohol wipes for those sharing equipment, as well as an educational program for health care workers, patients, and patients’ relatives,” he reported.

The researchers encouraged the culture change with a promotional drive that included coffee-break seminars, quizzes with prizes, a newsletter on hand hygiene, and the attachment of notices to staff’s pay advice slips. They devised slogans to remind people about hand hygiene, and even hired an advertising consultant to maximize the effect of the message.

They also held feedback sessions with senior nurses on sentinel wards to provide them with information on recent outcome data, and conducted medical, surgical, and nursing grand rounds on MRSA. A key component of the program was the development of a computer-based educational package that could be accessed online.

These and other culture change procedures were maintained and used in the 2-year multicenter study of four hospitals in metropolitan Melbourne, and in two regional hospitals. The program was coordinated by staff at Austin Health and the Victorian Quality Council in Melbourne, and funding was provided by the Department of Human Services for the state of Victoria, which backs efforts to control the MRSA “superbug.”

The primary outcome measures were rates of hand-hygiene compliance measured at 3- and 6-month intervals, and of MRSA disease—including bacteremia and clinical isolates—per 100 patient discharges measured at 1-month intervals, said Dr. Grayson.

“For all six sites, hand-hygiene compliance rose from 21% at baseline to 47% at 2 years. We identified the same significant improvements in MRSA disease rates that we identified in the single-center Austin study,” he said, noting that MRSA bacteremia fell from 0.03 to 0.01 per 100 patient discharges, and clinical isolates fell from 1.12 to 0.8 per 100 discharges.

“We were able to show that during the 2-year program, there were 719 fewer isolates than would have been expected had we not intervened. More importantly, MRSA bacteremia rates were roughly halved, with 60 fewer patients developing bacteremia than we would have otherwise expected,” Dr. Grayson said at the meeting, which was sponsored by the American Society for Microbiology.

The results of a cost analysis suggest that the culture change produced a potential savings over the 2-year period of at least $1.5 million. “The program cost roughly $750,000, so this was a 2-to-1 multiplier effect in terms of savings,” he said.

“This study shows that a coordinated hand-hygiene program that does not involve direct observation can improve compliance in both rural and urban health care settings and bring significant reductions in MRSA infection rates,” concluded Dr. Grayson.

A Swiss researcher, Dr. Hugo Sax, said that although such studies show that progress is being made in hand hygiene, optimal rates of compliance will be achieved only if more physicians lead by example.

“We have to address and educate different health care populations with tailored approaches instead of a one-size-fits-all approach,” said Dr. Sax, a consulting physician at the University Hospital in Geneva.

But first, physicians must align their own thinking toward patient safety, he said in an interview.

Dr. John M. Boyce, chief of infectious diseases at the Hospital of Saint Raphael in New Haven, Conn., agreed. “The evidence that hand hygiene reduces the spread of MRSA and other organisms is compelling, and we have to convince our physician colleagues that using alcohol hand rubs both before and after each patient visit doesn’t slow down their daily routines,” he said in an interview.
Automatic Epinephrine Injectors: A Change in Perspective From the Pulmonologists’ Standpoint?

Omalizumab treatment and anaphylaxis risk may be the biggest catalyst for this change in perspective.

As the list of biological agents grows, we can expect further increases in anaphylactic episodes. Thus, interest in managing anaphylactic events may also increase.

With the increased risks associated with the administration of in-office biological modifiers and monoclonal antibodies, it might be expected that the observations with omalizumab may only be the first in a series of such instances. For example, anaphylactic reactions to α-antitrypsin administration have been well-documented.

As the list of biological agents grows, we can expect further increases in anaphylactic episodes. Thus, pulmonologists’ interest in management of anaphylactic events, especially in the use of AEs, may also increase.

Citation for Administration of Epinephrine for Anaphylaxis

The National Institutes of Health and The Food Allergy and Asthma Network recently convened a panel to define criteria mandating the administration of epinephrine in patients presenting with a possible anaphylactic event. In the absence of the administration of a known allergen, it was suggested that a two-organ system presentation was required. For example, cutaneous manifestations plus respiratory symptoms, or cutaneous manifestations plus hypotension would normally be necessary.

However, in the presence of a known provocative agent, eg, omalizumab, only a single-organ system was needed to prompt the immediate use of epinephrine. For example, a patient manifesting only urticaria, receiving a known provocative agent, would be a candidate for the immediate administration of epinephrine.

Thus, the threshold for the administration of epinephrine in the outpatient setting is lowered in a patient who has been administered a drug, such as omalizumab, that might provoke an anaphylactic event.

It is emphasized, once again, that patients should be educated in the manifestations of anaphylaxis and be prepared to administer epinephrine immediately should any of these manifestations appear. It is well recognized that the rapid treatment of anaphylaxis with epinephrine can deter fatalities (Lieberman. Curr Opin Allergy Clin Immunol 2003; 3:313).

In view of the above observations, the perspective of the pulmonologist on prescribing AEs to patients may be changing. It would behoove physicians to be familiar with the injectors that are available for use.

AEIs Available in the United States

There are two AEs available for use in the United States: the EpiPen (Dey L.P.; Napa, CA) and the Twinject (Versus Pharmaceuticals, Inc.; San Diego, CA). The physician prescribing AEs needs to be aware of certain principles that are necessary for the successful use of these devices:

➤ Patients must be trained meticulously in their use. It is well known that many physicians prescribing AEs have not been familiar with the proper technique of administration; therefore, they have instructed patients incorrectly, resulting in improper use in the field. Also, patients who are not trained properly have been reluctant to use these devices, which dangerously delays therapy (Lieberman. Curr Opin Allergy Clin Immunol 2003; 3:313).

➤ Patients should be prescribed two doses, because up to 30% of anaphylactic events require two injections. EpiPen is available in a two-pack, and Twinject comes with two injections packaged together. Prescriptions should be written either for an EpiPen two-pack or a Twinject.

➤ Patients should be instructed as follows:

Upon the first sign that an allergic event is occurring, administer the epinephrine, and proceed to the nearest medical facility or call 911. If symptoms have not improved within 5 to 10 min, and you have not yet reached the medical facility or you have not yet been visited by emergency medical services, administer the second injection. From the above, it is clear that the physician prescribing an AEI needs to be familiar with the device chosen. There are differences between these devices.

As noted, the Twinject comes with two doses contained within a single prescribed package. However, the second dose is not delivered as an automatic injection but by the traditional "push plunger-syringe technique." The second dose is a traditionally filled syringe. Therefore, the patient must be instructed in two different techniques.

Both doses of the EpiPen are given by automatic injectors. Both devices are available in 0.3 mg (adult) and 0.15 mg (child) doses.

Summary

There are two contexts in which pulmonologists might consider use of an AEI. One can consider using an injector in the very brittle, severe asthmatic who suffers from acute, life-threatening episodes of bronchoconstriction. One also should consider an AEI in patients who have been administered omalizumab or, for that matter, any drug that may cause anaphylaxis.

Two types of AEsIs are available. Regardless of which one is chosen, it is essential that the patient is carefully instructed in the use of the injector and taught to recognize the signs and symptoms of anaphylaxis. The injector should be used in the outpatient setting at the first sign of an anaphylactic event.

Dr. Philip Lieberman
Clinical Professor of Medicine and Pediatrics
University of Tennessee, College of Medicine
Memphis, TN

Disclosure: Dr. Lieberman has served on the advisory board and as a consultant for Dey Laboratories and Versus Pharmaceuticals.

Dr. Gene L. Colice, FCCP
Editor, Pulmonary Perspectives
I have decided, with this as my first column for CHEST Physician, to give you an idea about who I am and what my goals are for my ACCP presidency. I am most honored and humbled to be the 70th President of the American College of Chest Physicians. I am a native of Philadelphia, Pennsylvania, and I am an only child. I am married to Zorita Duckworth-Thomas. I have four children (all adults), eight grandchildren, and one great grandchild. I attended eight grandchildren, and one have four children (all adults), Zorita Duckworth-Thomas. I am an only child. I am married to Zorita Duckworth-Thomas. I have four children (all adults), eight grandchildren, and one great grandchild. I attended undergraduate school at the University of Pennsylvania, Howard University College of Medicine, and completed my internal medicine and pulmonary fellowship training at the University of Michigan. My pulmonary fellowship experience at Michigan was also special. For the first and last time, I worked in a dedicated Respiratory Critical Care Unit with a one-to-one nursing-patient ratio—an unusual experience nowadays! Then moved from Michigan to Los Angeles to work at the Martin Luther King Jr. /Charles Drew Medical Center in the Watts community, a largely minority (Black and Hispanic), poor, and underserved community. It was the first opportunity I had to really work closely with and contribute to the care of underserved patients.

While at the King/Drew Medical Center, I worked closely with Dr. Albert H. Niden, FCCP, Chief of Pulmonary, and grew academically and professionally. Dr. Niden, along with Dr. Ben Burrows, was an early contributor to the COPD literature when he was at the University of Chicago.

While at King/Drew, I also served as program director for the internal medicine residency program. That experience helped me gain a better understanding of the US medical education system, and it substantially strengthened my interpersonal and administrative skills.

After 13 years at King/Drew, I moved back to Howard to serve as Chief of the Pulmonary Division. Because of my experience at Howard, I am more deeply committed to the care of underserved and minority patients, and I am aware of the absolute need for more minority physicians (especially Black and Latino physicians) in academic and community pulmonary, critical care, and sleep medicine.

I feel privileged to be President of the ACCP, a dynamic organization committed to “focused” care of patients and the education of its membership. I am fully supportive of all ACCP programs and intend to use my expertise to help each grow. Additionally, I am committed to better understanding the issues contributing to disparities in health and health care for the underserved and minority patients with pulmonary, critical care, and sleep-related illnesses and raising awareness of these issues in the College and the pulmonary, critical care, and sleep community, as a whole.

I believe disparity issues must become a part of the “cultural fabric” of the College. Whenever an educational or medical initiative is proposed by a College Institute or Network, it should be determined if there are related disparities in health or health care, and these issues should be discussed as part of the overall program submission. Disparity issues should also be a priority in CHEST and in the research and advocacy efforts of the College.

The CHEST Foundation has been quite active in supporting programs that are committed to the care of the underserved, and these efforts continue. I am convinced that the commitment of the College to the above issues and other substantial and dynamic programs will make the ACCP even stronger and more successful.

Again, I am most happy to be your 70th President, and I am totally committed to the continued growth and success of our ACCP.

### CELEBRATION OF PEDIATRIC PULMONOLOGY 2008

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**ACCP at ERS—Another Big Success!**

**By Joyce Bruno Reitzner, MBA, MPH**

Senior QI Research Analyst

This year’s European Respiratory Society (ERS) meeting provided another excellent opportunity for the ACCP to service its international members and chest physicians around the world. The 2007 ERS Congress was held in Stockholm, Sweden, September 16-19, 2007. Meeting attendance this year exceeded 15,000, with strong representation from Europe, Asia, and the Middle East. Currently, more than 17% of ACCP members are from countries outside the United States and Canada, and many of them attend this meeting.

For more than 10 years, the ACCP has “set up shop” at the annual ERS meeting to provide one-on-one membership service to many of these international members. The ACCP booth also gives these members the opportunity to peruse a variety of educational resources pertinent to their local practice. The most in-demand resources at ERS were the full spectrum of ACCP board review books and CD-ROMs and the ACCP-SEEK series. Aside from servicing members, the ACCP booth provides a venue for international physicians to meet and network with ACCP leadership, colleagues, and other members. If you attend the ERS next year, please be sure to visit the ACCP booth.

This year, the ACCP is providing a new service to the international ACCP membership. The ACCP has unveiled a new online application for international members to seek ACCP endorsement, faculty, or pro bono support for a medical education meeting in their country. The ACCP is accepting proposals for medical education meetings taking place July 1, 2008, through June 30, 2009. The application deadline is December 1, 2007.

For more information, visit www.chestnet.org/education/program/international.php.
Patient Safety in Critical Care

Critical care medicine is a significant issue, how does a provider start to improve patient outcomes? A culture of safety succeeds only in a multidisciplinary cooperative team environment. These teams must consist of doctors, nurses, residents, managers, and administrators delineating responsibilities for effective communication, monitoring results, and initiating pathways to improve safety. Medical errors are often system errors rather than individual errors, and ending a culture of blame is crucial. Tools used by industry and now in medicine are helpful in changing these attitudes. Failure mode and effects analysis (FMEA), and root cause analysis (RCA) are two of these tools. RCA is generally retrospective and is very effective. FMEA is generally proactive, which appears to be better. After successful implementation in the Veterans Affairs system in 2001, The Joint Commission is incorporating FMEA into its standards. Many interventions have been suggested, including ICU organization (open, closed, or mixed), ICU staffing, work hours, environment, protocols, daily goal sheets, and technologic standards. All have been introduced with varying results.

In the New York City Health and Hospital Corporation (NYCHC), a critical care collaborative committee representing 11 institutions and the largest public health complex in the country, has been working to improve safety and outcomes. NYCHC has joined and adapted the Institute for Healthcare Improvement’s campaigns, including “Saving 100,000 Lives,” “Protecting 5 Million Lives from Harm,” and “Surviving Sepsis.” Recent publications and presentations (Berlin et al, Venkatram et al. Presented at: American Thoracic Society annual meeting; May 22, 2007, San Diego, CA) have demonstrated that the implementation of daily goal sheets, vent bundles, tight glycemic control, central line bundles, and training videos have decreased events affecting patients significantly, with more reports to follow. In an effort to make safety and quality performance transparent to the general public, safety data are available at www.nyc.gov/ltc.

This article is the first in a series discussing possible solutions to patient safety concerns and improvement of patient care and outcomes.

References

ACCP Product of the Month: Audio Sessions From CHEST 2007

If you missed the opportunity to listen to an important clinical education session update at CHEST 2007 in Chicago, place your order for audio sessions today. Simply download sessions to your computer, memory stick, or MP3 player to receive information and training resources you can use as a reference or share with your professional team.

To order, visit www.dcprowsonline.com/accp and click on the “Sessions Available” link. All sessions can be purchased individually. If you need a memory stick for storing the audio sessions, you also may want to purchase the ACCP/DCP memory stick pen.
Head-of-Bed Monitoring Improves Positioning Compliance

BY MITCHELL G. KAYE, MD, FCCP

V entilator-associated pneumonia (VAP) is a common med-
ical problem with significant consequences. It complicates the course of almost 30% of patients sup-
ported by mechanical ventilation, and it is a leading cause of death among hospital-acquired infec-
tions, with a mortality rate that approaches 50%. Semirecumbent positioning has been shown to decrease the inci-
dence of VAP yet patients often do not have the head-of-bed (HOB) consistently elevated.

The purpose of this study was to determine whether continuous HOB monitoring using an indicator light increases the amount of time patients supported by mechanical ventilation have the HOB elevated above 30°.

This study was performed in a 30-bed ICU at Abbott Northwestern Hospital in Minneapolis, MN. Ninety patients sup-
ported by mechanical ventilation were enrolled in this controlled, prospective study.

An electronic sensor attached to the bed frame provided continuous monitor-
ing and recording of HOB angle; whenever HOB was >30, the sensor activated a bright green vertical light and timer on the monitor device.

For the group of control subjects, the light was disabled, the monitor was stored out of view, and the nursing staff was blinded to the time measurements. For the intervention group, connec-
tions to the light were enabled and...
the monitor placed on top of the ventilator, where the light and timer were clearly visible to the nursing staff.

The percentage of time with HOB elevated > 30 degrees was significantly greater (p<0.0001) in the intervention group, with a median of 81% vs a median of 17% in the group of control subjects.

The efficacy of the monitor device appeared to be related to the indicator light, which was visible from anywhere in the patients’ rooms, as well as from outside the room through the doorway or window.

The light served as a visual cue that did not compete with other alarms and provided positive reinforcement to the nursing staff to maintain proper HOB elevation.

Continuous HOB monitoring using an indicator light significantly increases the time patients supported by mechanical ventilation have the HOB elevated > 30 degrees.

By effectively encouraging and reliably measuring compliance with semi-recumbent positioning, continuous HOB monitoring appears to be a valuable clinical tool in the overall care of patients receiving mechanical ventilation support.

Further research is needed to determine whether continuous HOB monitoring, as part of a comprehensive prevention program, can contribute to a significant decrease in the incidence of VAP.

For more information, Dr Kaye’s slide presentation is posted under “Hot Topics” at www.chestnet.org/networks/critical_care/hotTopics.php.

Please see a brief summary of prescribing information including boxed WARNING on the next page.

### Table 3. THE-PRINCE Safety Data

<table>
<thead>
<tr>
<th></th>
<th>LOVENOX® n=239*</th>
<th>UFH n=212*</th>
<th>Fisher’s Exact Test (2-tailed) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events (DVT or PE), n (%)</td>
<td>20 (8.4)</td>
<td>22 (10.4)</td>
<td>0.015</td>
</tr>
<tr>
<td>Total events among patients with severe respiratory disease</td>
<td>9 (7.1)</td>
<td>7 (5.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>5 (1.5)</td>
<td>12 (3.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Hematoma at injection site (&gt;5 cm)</td>
<td>24 (7.2)</td>
<td>42 (12.6)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

NS, not significant. *Evaluable

## In a Comparative Trial, LOVENOX® Had Similar Efficacy to UFH

The Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin (THE-PRINCE) study was a multicenter, controlled, randomized, open-label study of LOVENOX® against UFH for the prophylaxis of DVT and PE in 2 patient groups: patients with heart failure (333 randomized) and patients with severe respiratory disease (332 randomized). After 10±2 days of prophylaxis, there was an equivalent incidence of DVT/PE in the LOVENOX® group vs UFH (8.4% vs 10.4%, P=0.015) (Table 3). Among the patients with severe respiratory disease, the incidence of DVT/PE was 7.1% in the LOVENOX® group and 5.9% in the UFH group, a difference that was not statistically significant.

Overall, there were fewer bleeding complications in the LOVENOX® group (115 vs 3.6% for UFH), although this difference also was not statistically significant. However, there was a significantly lower incidence of injection-site hemorraghe in the LOVENOX® group (7.2% vs 12.6% for UFH).

## Appropriate DVT/PE Prophylaxis Benefited Hospitalized Patients With Acute Respiratory Diseases Including COPD Exacerbation

Large, randomized clinical trials demonstrated that appropriate prophylaxis with LOVENOX® reduced the risk of DVT and PE in acutely ill medical patients with severely restricted mobility. LOVENOX® was as effective as UFH in this population and has advantages in safety and convenience.

## IMPORTANT SAFETY INFORMATION

LOVENOX® (enoxaparin sodium injection) cannot be used interchangeably with other low-molecular-weight heparins or unfractionated heparin, as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

When epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low-molecular-weight heparins or heparinoids are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of postoperative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis. Patients should be frequently monitored for signs and symptoms of neurological impairment (see WARNING).

As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Dosage adjustment is recommended in patients with severe renal impairment. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX® therapy. Bleeding can occur at any site during LOVENOX® therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site (see WARNINGS and PRECAUTIONS).

Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia, LOVENOX® should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, LOVENOX® should be discontinued. Cases of heparin-induced thrombocytopenia have been observed in clinical practice (see WARNINGS).

The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women or in women with mechanical prosthetic heart valves (see WARNINGS).

LOVENOX® is contraindicated in patients with hypersensitivity to enoxaparin, heparin, or pork products, and in patients with active major bleeding.

## REFERENCES

Lovenox Injection (enoxaparin sodium injection) is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin. Lovenox Injection is not intended for intramuscular administration.

Mechanical Prosthetic Heart Valves:

Lovenox Injection is contraindicated in patients with mechanical prosthetic heart valves and has not been adequately studied in pregnant women. There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies have not been conducted with Lovenox Injection. There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies have not been conducted with Lovenox Injection. There are no adequate and well-controlled studies in pregnant women with mechanical prosthetic heart valves. The use of Lovenox Injection in pregnant women should be reserved for women with mechanical prosthetic heart valves who are at high risk for thromboembolism (see WARNINGS, Mechanical Prosthetic Heart Valves). The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse reactions include thromboembolic events, and adjusting of dosage may be needed. Although a single-dose injection is usually adequate for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin, Lovenox Injection must be administered during pregnancy. Careful attention to dosing intervals and concomitant medications (especially anticoagulants and platelet inhibitors) should be mainstays of therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa activity should be measured. If co-administration is essential, conduct close clinical and laboratory monitoring.

CONTRAINDICATIONS:

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with recent (within 14 days) intracranial hemorrhage, or in patients with mechanical prosthetic heart valves and has not been adequately studied in pregnant women. There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies have not been conducted with Lovenox Injection. There are no adequate and well-controlled studies in pregnant women with mechanical prosthetic heart valves. The use of Lovenox Injection in pregnant women should be reserved for women with mechanical prosthetic heart valves who are at high risk for thromboembolism (see WARNINGS, Mechanical Prosthetic Heart Valves). The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse reactions include thromboembolic events, and adjusting of dosage may be needed. Although a single-dose injection is usually adequate for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin, Lovenox Injection must be administered during pregnancy. Careful attention to dosing intervals and concomitant medications (especially anticoagulants and platelet inhibitors) should be mainstays of therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa activity should be measured. If co-administration is essential, conduct close clinical and laboratory monitoring.

WARNINGS: Mechanical Prosthetic Heart Valves

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DOSAGE AND ADMINISTRATION:

In patients undergoing knee replacement surgery; in patients undergoing abdominal surgery who are at risk for thromboembolic events; and in patients with mechanical prosthetic heart valves. The prophylaxis of thromboembolism should be administered during pregnancy. Careful attention to dosing intervals and concomitant medications (especially anticoagulants and platelet inhibitors) should be mainstays of therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa activity should be measured. If co-administration is essential, conduct close clinical and laboratory monitoring.

Thrombocytopenia:

Thrombocytopenia should be treated with cessation of Lovenox Injection. The administration of Lovenox Injection should be reinitiated if the platelet count returns to normal levels. The incidence of major hemorrhagic complications during Lovenox Injection treatment has been low.

Hemorrhage:

Hemorrhage during treatment with Lovenox Injection should be managed by dose reduction. If major hemorrhage occurs, Lovenox Injection therapy should be discontinued. If a major hemorrhagic complication occurs, therapy with Lovenox Injection should be stopped and replaced with alternative treatment. If the patient is on treatment with Lovenox Injection, monitoring of the anti-Factor Xa activity during treatment with Lovenox Injection should be discontinued.

CLINICAL PHARMACOLOGY:

Lovenox Injection is a low-molecular-weight (5500-8500 daltons) heparin produced through recombinant technology. Lovenox Injection is a thiodiazo analog of heparin, a natural antithrombotic substance. Lovenox Injection is associated with a fatal “Gasping Syndrome”. Because benzyl alcohol may be irritant to the eye, the multi-dose formulation of Lovenox should not be used and the single-use vials should be used.

LABORATORY TESTS:

Lovenox Injection does not interfere with the determination of platelet count or platelet function tests. Lovenox Injection does not affect the levels of fibrin degradation products (FDPs). If the evaluation of these cases. Regarding the development of labor for women with mechanical prosthetic heart valves. Lovenox Injection is not intended for intramuscular administration.

Drug Interactions:

While not adequately studied, pregnant women with mechanical prosthetic heart valves should not be treated using the multi-dose formulation of Lovenox. Drug Interactions: Lovenox Injection is not intended for intramuscular administration.

Pediatric Use:

Lovenox Injection is not intended for intramuscular administration. Pediatric Use: Lovenox Injection is not intended for intramuscular administration.

CONCEIVED-TO-CONCEIVE:

Lovenox Injection is not intended for intramuscular administration.

CONTRACEPTION:

Lovenox Injection is not intended for intramuscular administration.

CONTRAINDICATIONS:

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clinical databases. These databases acquire, collate, and analyze information to ultimately help physicians fulfill national and local requirements, identify areas where their practice patterns differ from national benchmarks, and determine why.

The concept of clinical databases is not new. The Society of Thoracic Surgeons National Database and National Surgical Quality Improvement Program database, which focuses on surgical procedures, have existed for more than a decade, starting in the Veterans Affairs medical system and expanding to the nongovernmental sector. The University HealthSystem Consortium provides its members with the opportunity to participate in a database encompassing clinical and administrative domains. Data quality, aggregation methods, and information vary across databases. However, the aim of all the databases is to help physicians improve patient care and outcomes while minimizing their practice cost.

Despite this surge in clinical databases, there is a need to capture and aggregate information from pulmonary, critical care, and sleep medicine, while streamlining the reporting burden for individual physicians and enabling them to satisfy pressing administrative requirements to deliver the best quality patient care.

With the guidance of the ACCP Board of Regents, the Quality Improvement Committee has initiated the development of a clinical database for chest medicine physicians for use by ACCP members. In the spring of 2008, the ACCP plans to initiate the pilot phase of the database, which will allow physicians to self-assess competency and practice gaps, benchmark their practices with reliably and clinically relevant information, access more targeted educational interventions, maintain certification of management and credentialing requirements, and develop local quality improvement programs.

For details about ACCP quality improvement efforts, please contact Joyce Bruno Reizewitz, MFA, MPH, at jbruno@chestnet.org.

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**LOVENOX® (enoxaparin sodium injection)**

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Oral or IV Prednisolone in the Treatment of COPD Exacerbations: A Randomized, Controlled, Double-Blind Study. By Dr. Y. de Jong, et al.

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Responsibilities of Authorship. By Dr. W. M. Ylvisaker.

www.chestjournal.org
Introducing the New Ambassadors Group Chair

The CHEST Foundation’s Ambassadors Group is pleased to introduce Zorita Thomas as the Ambassadors Group Chair for 2007-2008. Zorita was born in Cassopolis, MI, and has a large family. She attended Andrews University in Berrien Springs, MI, where she majored in vocal music. She has a special interest in Negro spiritual music and has recorded her first CD entitled *Forget Me Not, Negro Spirituals by Zorita.*

Zorita also uses her time as a hospice-care volunteer. When asked what goals and objectives she has set for the Ambassadors Group for the upcoming year, she responded that she would like to see Ambassadors Group members expand and strengthen their reach to more youth, particularly in the area of lung health education. She would like to see follow-up with students who have been taught the Lung Lessons™ curriculum. Zorita feels that since smoking starts at a young age, more effort should be made to develop higher self-esteem in youth so that they never start smoking. In addition, Zorita would like more ACCP members to be part of the Ambassadors Group so that they can be involved in the lung health education efforts of the group.

**Educational Sleep Slide Kit**

The Sleep Medicine Network of the American College of Chest Physicians developed an educational slide kit to (1) educate members of the College about sleep medicine, and (2) help members of the Sleep Medicine Network use their expertise to teach others about the important aspects of sleep medicine. These slides may also serve to help those who are preparing for certification examinations in sleep medicine.

The slides have been authored by national experts in the field who are excellent, experienced teachers. Educating physicians who are not trained in sleep medicine about this subspecialty will allow more rapid diagnosis and therapy for patients and increase access to specialized care, as needed.

In the United States population, there is a prevalence of about 5% for sleep apnea, 10 to 20% for insomnia, and 3 to 15% for restless legs syndrome. Similar findings are found throughout the world. Some 40 million Americans suffer from excessive sleepiness or difficulty sleeping. Sleep disorders may lead to impaired work performance, lost productivity, increased motor vehicle and other types of accidents, and an increased risk of cardiovascular disease (with sleep apnea).

Members of the ACCP Sleep Medicine Network are among the leaders in becoming the primary subspecialists who identify and treat patients with sleep disorders. This newly posted Educational Sleep Slide Kit (www.chestnet.org/networks/presentations/Sleep) will allow physicians to better serve their patients, thus resulting in improved health and quality-of-life.

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PRACTICE MANAGEMENT UPDATES
Share New Codes With Practice Staff

BY DIANE KRIER-MORROW, MBA, MPH, CCS-P

The College leadership was pleased with the significant work of its committees this past year. The Practice Management Committee (PMC), chaired by Richard M. Hamrick III, MD, MBA, FCCP; includes the ACCP CPT Advisor, Steve G. Peters, MD, FCCP; and the ACCP RUC Advisor, Scott Man-aker, MD, PhD, FCCP. The ACCP partners with ATS representatives, including the ATS CPT Advisor, Stephen Hoffmann, MD, FCCP; and the ATS Practice Committee Chair and RUC Advisor, Alan L. Plummer, MD, FCCP.

New Codes
The Practice Management Committee met on October 22 and was pleased to hear of the significant number of preprint orders for the 12th edition of the ACCP coding and practice management book, renamed Coding for Chest Medicine 2008: A Practice Management Tool.

There are several coding changes this year related to pulmonary medicine.

Smoking Cessation Counseling
The Medicare smoking cessation codes are transitioning into CPT; it is important for members to ask their patients to request this benefit from other third-party payers. Patients are more likely to stop tobacco use when they are encouraged by their physicians.

Most pulmonologists provide this service, yet the vast majority is not using these codes.

The codes listed in the sidebar below are reported in addition to an evaluation and management code, appended with modifier 23. Smoking cessation counseling less than 3 minutes is included in the E/M code.

Medicare will cover a total of eight sessions in a 12-month period. Medicare requires the medical record to show medical necessity. Use appropriate ICD-9-CM diagnosis codes, such as 492.8 Tobacco dependence and 492.8 Emphysema.

Dr. Peters recommends that counseling be documented and smoking cessation modalities discussed, along with the medical condition or therapeutic agent that is adversely affected by tobacco use.

Lungs and Pleural Codes Renumbered
In addition, CPT renumbered five codes in the Lungs and Pleural subsection of the Surgery/Respiratory section of CPT.

The practice will have significant payment denials if you do not use the new numbers listed after January 1 for thoracentesis, insertion of pleural catheter, tube thoracostomy, and chemical pleurodesis.

New Subcutaneous Infusion Codes
For physicians working in the allergy field, there are three new codes, 90769-90771, for subcutaneous infusion of immune globulin.


To purchase your copy of the book, call (800) 343-2227 or order online at www.chestnet.org.

### New 2008 CPT Codes

<table>
<thead>
<tr>
<th>New 2008 CPT Code</th>
<th>2007 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99406 60375</td>
<td>Smoking and tobacco use cessation counseling visit; intermediates, greater than 3 minutes, up to 10 minutes</td>
<td></td>
</tr>
<tr>
<td>99407 60376</td>
<td>Smoking and tobacco use cessation counseling visit; intensive, greater than 10 minutes</td>
<td></td>
</tr>
<tr>
<td>32421 32000</td>
<td>Thoracentesis, puncture of plural cavity for aspiration, initial or subsequent</td>
<td></td>
</tr>
<tr>
<td>32422 32002</td>
<td>Thoracentesis with insertion of tube, includes water seal (eg: for pneumothorax), when performed (separate procedure)</td>
<td></td>
</tr>
<tr>
<td>32560 32005</td>
<td>Chemical pleurodesis (eg: for recurrent or persistent pneumothorax)</td>
<td></td>
</tr>
<tr>
<td>32550 32019</td>
<td>Insertion of indwelling tunneled pleural catheter with cuff</td>
<td></td>
</tr>
<tr>
<td>32551 32020</td>
<td>Tube thoracostomy, includes water seal (eg: for abscess, hemothorax, empyema), when performed (separate procedure)</td>
<td></td>
</tr>
<tr>
<td>90769</td>
<td>Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to one hour, including pump set-up and establishment of subcutaneous infusion site(s) (For infusions of 15 minutes or less, use 90772)</td>
<td></td>
</tr>
<tr>
<td>90770</td>
<td>Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure) (Use 90770 in conjunction with 90769) (Use 90770 for infusion of intervals of greater than 30 minutes beyond one-hour increments)</td>
<td></td>
</tr>
<tr>
<td>90771</td>
<td>Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure) (Use 90771 in conjunction with 90769) (Use 90769 and 90771 only once per encounter)</td>
<td></td>
</tr>
</tbody>
</table>

Source: ACCP Practice Management Committee
BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — Children aged 3-13 years who were seropositive for Helicobacter pylori were 35% less likely to have ever had asthma, compared with those who were seronegative for the bacteria, reported Dr. Blaser, chairman of the department of medicine and professor of medicine and microbiology at NYU. They were also 44% less likely to have asthma before the age of 5 years.

In addition, the researchers found that children aged 3-13 who were seropositive for H. pylori were 51% less likely to have ever had asthma, 60% less likely to have current asthma, and 71% less likely to have current allergic rhinitis, compared with children who did not carry the organism in their stomachs.

He added that the protective relationship observed between asthma, allergic rhinitis, eczema, and skin sensitization among the seropositive study participants suggests an immunologic mechanism of action. “The speculation is that the relationship is immunologically based,” said Dr. Blaser, who is a past president of the IDSA.

Dr. Blaser noted that 50 years ago more than half of children in the United States had H. pylori in their stomachs. Today, fewer than 1 in 10 children under the age of 13 carry the bacteria in their stomachs.

The finding comes from the United States Pediatric Multicenter Pneumococcal Surveillance Study Group, a network of eight children’s hospitals that has been identifying patients with systemic pneumococcal infections since 1993. The researchers send the isolates to a central laboratory for serotyping and complete a standardized case report form that includes demographic and clinical information, including the number of 7-valent pneumococcal conjugate vaccinations (PCV7) the child has received.

At the annual meeting of the Infectious Diseases Society of America, Dr. Sheldon L. Kaplan reported on 1,234 isolates collected between April 1, 2000 and December 31, 2006. Ages of patients ranged from 0 to 20 years of age, but most infections occurred in the first 5 years of life. Serotype 19A accounted for 19% of all nonvaccine serotype isolates in 2000, 22% in 2001, 18% in 2002, 23% in 2003, 39% in 2004, 34% in 2005, and 49% in 2006. Serotype 19A has been the most common nonvaccine serotype each year since 2003. In 2005 and 2006 combined, the next most common nonvaccine serotypes were 1 (21 cases), 3 (14 cases), 33, 15, and 7 (13 cases each), and 6A (11 cases).

No deaths were reported associated with pneumococcal infections in 2006. The number of invasive infections reached its lowest point in 2004 and then increased 13% in 2005 and another 5% in 2006.” Dr. Kaplan, chief of the infectious disease service at Texas Children’s Hospital, Houston, noted in a later interview “Nevertheless, the number of cases annually was still 60% less than seen each year before the pneumococcal conjugate vaccine was licensed for routine administration to infants.”

The most common type of infection among children with serotype 19A was bacteremia, followed by pneumonia, bacterial meningitis, and other infections.

When the researchers applied the 2007 breakpoints for minimum inhibitory concentration (MIC) interpretations, they found that 28% of 19A isolates in 2006 were susceptible to penicillin, 34% were immediately susceptible to penicillin, and 37% were resistant to penicillin.

Dr. Kaplan, who is also a professor of pediatrics at Baylor College of Medicine, Houston, predicted that the percentage of isolates resistant to penicillin “will go down dramatically” when the Clinical and Laboratory Standards Institute publishes new Streptococcus pneumoniae penicillin breakpoints for nonmeningococcal pneumococcal isolates in 2008.

He concluded that continued surveillance of invasive pneumococcal infections “will remain necessary following the inclusion of serotype 19A and other nonvalent serotypes.”

The United States Pediatric Multicenter Pneumococcal Surveillance Group includes clinicians from Texas Children’s Hospital, Houston; Children’s Hospital of Pittsburgh; Children’s Hospital San Diego; Columbus (Ohio) Children’s Hospital; Children’s Memorial Hospital, Chicago; Arkansas Children’s Hospital, Little Rock; Brenner Children’s Hospital, Wake Forest, N.C.; and Children’s Hospital Los Angeles.

Dr. Kaplan disclosed that he has received research grants from Roche and Wyeth Pharmaceuticals.

Eliezer Gonen, MD

The Science and Practice of Sleep Medicine

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — Serotype 19A may be the most common serotype isolated from children’s invasive pneumococcal infections in the United States, results from a multicenter study suggest.

The finding comes from the United States Pediatric Multicenter Pneumococcal Surveillance Study Group, a network of eight children’s hospitals that has been identifying patients with systemic pneumococcal infections since 1993. The researchers send the isolates to a central laboratory for serotyping and complete a standardized case report form that includes demographic and clinical information, including the number of 7-valent pneumococcal conjugate vaccinations (PCV7) the child has received.

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Improving insulin sensitivity, lower postprandial glucose may be benefits of treating sleep apnea.

By Miriam E. Tucker

Elsvier Global Medical News

MINNEAPOLIS — The need to unite sleep specialists from multiple academic departments challenges the field of sleep medicine, Dr. Ronald D. Chervin said at the annual meeting of the Associated Professional Sleep Societies.

“Because sleep is relevant to so many different departments, there is not always good integration across campuses,” Dr. Chervin, a professor of sleep medicine, a pediatric sleep and behavior clinic and anesthesiology, and director of the sleep disorders center at the University of Michigan, Ann Arbor, said.

For example, a sleep scientist may not rub elbows daily with a pulmonologist or ENT specialist, he said.

The structural challenges that persist at many research universities can make interdisciplinary integration difficult, even though such integration may be the way to provide the best patient care, Dr. Chervin noted.

But the tug of war between clinicians desires to provide good multidisciplinary care versus departmental concerns for the bottom line.

Most sleep specialists agree that patients receive the best care when they see clinicians from a variety of medical fields, Dr. Chervin said.

But sharing human resources is not always a priority for any given academic department, and it is not always easy to join billing opportunities to another department in order to serve a higher goal and allow faculty to pursue research interests, he explained.

The role of sleep medicine can be difficult to explain to administrators and faculty outside the field, in part because there often is inadequate investment in sleep medicine specifically.

For example, even at the University of Michigan, which has a large and successful sleep disorders center, there is no administrator dedicated to sleep medicine to help the director manage budgets and financial spreadsheets, “which we are not trained in medical school to do,” Dr. Chervin said.

Also, billing and hiring issues still create interdepartmental friction. “I’m proud of our faculty here at Michigan, but we have lost some opportunities to hire qualified personnel because of these departmental issues,” he said.

One strategy that the university has used to overcome some of the interdepartmental barriers has been the creation of an “interdisciplinary” clinic.

“We can see patients should to shoulder with an ENT specialist, maxillofacial surgeon, and dentist. It serves the patients’ interests and is wonderful for education,” he said.

And we managed to satisfy all the departments in terms of billing.” The university has developed two other clinics that follow the CPAP program model—a multidisciplinary pediatric sleep and behavior clinic and another behavioral sleep medicine center for adults.

What does the future hold for sleep medicine? Dr. Chervin said he believes that creating comprehensive sleep centers at universities would improve patient care and promote the basic scientific research that continues to drive advances in sleep medicine.

Ideally, a “center for sleep science” would unite specialists on campus, at least for joint grand rounds, for training, and for promoting grant submissions that could cross department boundaries, he said. In his view, sleep centers should uphold a tripartite mission that includes research, education, and patient care and provide both clinical and preclinical programs.

Sleep centers need their own physical space and dedicated funding, in part to allow them to bill for clinical and laboratory services and then reimburse other departments for faculty effort, Dr. Chervin said. As sleep centers should have a greater say in hiring decisions, he added.

As more data emerge to support the impact of sleep and sleep problems on a range of medical conditions, support for interdisciplinary work in sleep medicine and the establishment of sleep centers may gain traction.

“How does a new interdisciplinary field fit within a traditional, department-based academic medical center?” Dr. Chervin asked. “It’s like trying to put a square peg in a round hole.”

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Sleep Medicine Strives to Unite Multiple Disciplines

BY HEIDI SPLETE

Elsvier Global Medical News

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D A T A W A T C H

Who Pays for Personal Health Care?

Revised Modafinil Labeling Highlights Rash Risks

BY ELIZABETH MECHCATIE

W arnings about serious rashes—including Stevens-Johnson syndrome and hypersensitivity reactions—as well as psychiatric symptoms have been added to the label of modafinil, according to a MedWatch notice issued by the Food and Drug Administration on Oct. 24.

Modafinil, described as a “wakefulness-promoting agent,” is marketed as Provigil by Cephalon Inc., and was first approved as a treatment for narcolepsy in 1998. It is approved for improving wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift-work sleep disorder. It is not approved for any pediatric indications, the advisory emphasizes, although some reports have been in children.

The MedWatch notice and a “Dear Healthcare Professional” letter issued by Cephalon describe worldwide postmarketing reports of life-threatening rash, including toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) in adults and children. There have also been postmarketing reports of angioedema and multiorgan hypersensitivity reactions.

The reporting rate—which is considered an underestimate, because postmarketing reports of adverse events tend to be underreported—of TEN and Stevens-Johnson syndrome (SJS) associated with modafinil use is higher than the background incidence rate, according to the letter. The background in the general population is estimated at 1-2 million cases per million person-years.

The potential for benign rashes—which have been associated with modafinil use—develop into serious rashes cannot be reliably predicted, so “modafinil should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related,” the letter says.

Because of postmarketing reports of angioedema, the letter says that patients should be advised to stop treatment and contact their physician any signs of symptoms suggesting angioedema or anaphylaxis.

The letter also recommends that discontinuation of the drug should be considered in patients who develop psychiatric symptoms during treatment, because manic, anxiety, hallucinations, and suicidal ideation are among the psychiatric adverse reactions reported in people treated with modafinil.

The “Dear Healthcare Professional” letter says that in studies, the incidence of rash resulting in discontinuation of the drug in pediatric patients (younger than age 17 years) was 0.8% (11 of 1,385).

C L A S S I F I E D S

PROFESSIONAL OPPORTUNITIES

VA Palo Alto Health Care System (VAPACHS)

VA Palo Alto Health Care System (VAPACHS) invites applications for a staff physician in the Pulmonary, Critical Care Medicine, Sleep Disorders Section of the Medical Service. Applicants should be BC/BE in Pulmonary and Critical Care Medicine. Training in intervention- nal pulmonology and sleep disorders medicine is desirable. A commitment to academic achievement and teaching is expected. Research interest and experience are desirable. Qualified applicants may be eligible for a faculty appointment in the Clinical – Educator track in the Department of Medicine in the Stanford University School of Medicine. VAPACHS is committed to increasing the representation of women and members of minority groups on its staff and particularly encourages applications from such candidates. Applicants should fax an updated CV and 3 references to the attention of Rajinder Chitkara, MD, Chief, Pulmonary, Critical Care Medicine, Sleep Disorders Section at fax number: 650-852-3276 or mail to the attention of VAPACHS, 1111 Miranda Avenue, Palo Alto, CA 94304. The Department of Veterans Affairs is an equal opportunity employer.

PULMONARY, CRITICAL CARE, SLEEP MEDICINE PHYSICIAN

Openings exist at the VA Medical Center Milwaukee, Wisconsin, for physicians with strong academic credentials to join the Pulmonary, Critical Care and Sleep Medicine Program. Extensive research opportunities exist through the Medical College of Wisconsin. Qualified candidates should be board certified or eligible in Pulmonary and Critical Care Medicine and Sleep Medicine. A strong background in COPD, lung cancer and pulmonary infectious diseases, sleep medicine and critically ill patients is required. Clinical research experience, a history of academic achievement, teaching in undergraduate and graduate medical education, and participation in a significant publication record is also required. Applicants must have appropriate credentials for a faculty appointment at the Medical College of Wisconsin as an Assistant Professor level or higher. Finally, applicants must have a commitment to teaching residents and students, and attend on a general medical service. Questions may be directed to Ralph Schapira, M.D., ralph.schapira@va.gov. Send cover letter and C.V. to Marilyn Denning, (HR-05), Clement J. Zablocki VA Medical Center, 5000 W. National Ave., Milwaukee, WI 53295.

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the benefits of caffeine therapy for apnea of prematurity clearly outweigh the risks in the first large, randomized, placebo-controlled study to examine the risks and benefits of this long-used therapeutic approach. Caffeine therapy improves not just long-term survival, but also long-term survival without neurodevelopmental disability, according to the trial’s principal investigator, Dr. Barbara Schmidt at McMaster University, Hamilton, Ont., and her associates.

The results of the international study were published in the New England Journal of Medicine.

“The number of infants who would need to be treated with caffeine to prevent one adverse outcome was 16,” the investigators said. Caffeine therapy had no significant effect, however, on rates of death, severe hearing loss, or blindness. While caffeine and other methylxanthines have been used as respiratory stimulants for apnea of prematurity for over 10 years, these findings show for the first time that the benefits of caffeine therapy “outweigh any potential risks up to 2 years after very preterm birth,” the investigators said.

Without prospective study results, there were concerns that the drugs might adversely affect the development of the preterm brain and overall growth. Caffeine is known to reduce cerebral blood flow in adults; it can inhibit adenosine receptors, which might compromise brain-cell survival during hypoxia; and it can raise the metabolic rate and oxygen consumption, which might compromise long-term growth.

To address the concerns, Dr. Schmidt and her associates studied 1,869 infants who weighed 500-1,240 g at birth between 1999 and 2004 and were randomly assigned to receive intravenous caffeine therapy, which consisted of a loading dose of 20 mg/kg and a daily dosage of 5 mg/kg until infants reached a median premenstrual age of 35 weeks. Caffeine therapy significantly improved survival without neurodevelopmental disability to a corrected age of 18-21 months. Among neonates who had been randomly assigned to receive caffeine, the rate of death or survival with a disability was 40.2%, compared with 46.2% for those who had received placebo. The incidence of cerebral palsy was 4.4% in those given caffeine therapy, compared with 7.3% for placebo. The rate of apnea was seen in 33.8% of the caffeine-treated group, compared with 38.3% of the placebo group. Caffeine therapy was also associated with a reduced rate of severe retinopathy of prematurity (N. Engl. J. Med. 2007;357: 1893-1902).

Caffeine therapy allowed neonates to discontinue positive airway pressure therapy at an average of 1 week sooner than placebo did, and the investigators attributed most of the treatment’s benefits to this difference.

It is still possible that infants who received active treatment had better outcomes because they had fewer hypoxic-ischemic episodes due to apnea.

The researchers are continuing their follow-up of this cohort to a corrected age of 5 years so that they can assess possible longer-term effects on cognition, gross and fine motor function, vision, hearing, behavior, and general health.

In an editorial comment accompanying this report, Dr. David K. Stevenson of Stanford (Calif.) University said this investigation “provides needed support for a treatment approach that had already become routine clinical practice. In this case, physicians guessed correctly (or at least were lucky) that the benefits of caffeine therapy outweighed the risks, long before they had conducted the necessary trials to confirm this,” he said (N. Engl. J. Med. 2007;357:1967-8).

For many proposed treatments, we are not so lucky, and our randomized controlled trials debunk our preconceived notions, as in the cases of prenatal phenobarbital treatment (which failed to prevent intraventricular hemorrhage) and postnatal steroids (which failed to prevent bronchopulmonary dysplasia).
Zemaira® is indicated for chronic augmentation and maintenance therapy for adults with alpha 1-proteinase inhibitor (A1-PI) deficiency and emphysema. Clinical data demonstrating the long-term effects of chronic augmentation therapy with Zemaira® are not available. As with other Alpha-1 therapies, Zemaira® may not be appropriate for the following adult individuals as they may experience severe reactions, including anaphylaxis: individuals with a known hypersensitivity and/or history of anaphylaxis or severe systemic reaction to A1-PI products or their components and individuals with selective IgA deficiencies who have known antibodies against IgA.

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

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

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

* Shelf life purity specification is ≥90%.
† In a retrospective analysis in the pivotal clinical trial, Zemaira® patients were three times less likely to experience exacerbations of their COPD than Prolastin® patients.
‡ No clinically significant differences were detected between the treatment groups.
§ Based on recommended dosage as stated in the product package inserts of 60 mg/kg body weight at the infusion rate of 0.08 mL/kg/min.

Prolastin is a registered trademark of Talecris Biotherapeutics, Inc.

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