ACIP Picks Five Priority Groups for H1N1 Vaccination

Would cover 159 million Americans.

BY MIRIAM E. TUCKER
Elsevier Global Medical News

ATLANTA — Initial vaccination efforts against the novel influenza A (H1N1) should focus on immunizing as many people as possible in five target groups, while smaller subsets of some of those groups should be targeted if demand for vaccine exceeds supply. As more supply becomes available, the rest of the population should be targeted for vaccination.

Those recommendations were made by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention at a special 1-day meeting on July 29. Primary targets for novel influenza A (H1N1) immunization efforts include the following five groups, which together total approximately 159 million individuals in the United States. Current seasonal influenza coverage among these groups is only 20%-50%, said Dr. Anthony J. Fiore of the CDC’s Influenza Division.

• Group 1–Pregnant women. They have been found at higher risk for complications from seasonal influenza in past pandemics, and several deaths have been reported among pregnant women during the current 2009 pandemic. Vaccination of pregnant women also is seen as a way to potentially protect infants who cannot be vaccinated, via transfer of maternal antibodies to newborns.

• Group 2–Household contacts and caregivers for infants younger than 6 months of age. The aim of providing the vaccine to people who interact with infants is to produce a possible “cocooning effect,” providing indirect protection for the infants who are at risk of infection. This protection is most needed during the first 3 months after birth.

• Group 3–Young children (ages 6 months to 5 years). Those recommendations were made by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention at a special 1-day meeting on July 29. Primary targets for novel influenza A (H1N1) immunization efforts include the following five groups, which together total approximately 159 million individuals in the United States. Current seasonal influenza coverage among these groups is only 20%-50%, said Dr. Anthony J. Fiore of the CDC’s Influenza Division.

• Group 4–Young adults aged 18-49 years. Between 2007 and 2009, the CDC found that 46% of household contacts of seasonal influenza were among young adults. This group also is at high risk for complications from seasonal influenza and is expected to be at a high risk for complications from H1N1.

• Group 5–Persons 50 years and older. This group is at high risk for complications from seasonal influenza. Those who were vaccinated in recent years also are at high risk for complications from H1N1.

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Lung Cancer Maintenance Tx Approved

BY ELIZABETH MECHCUTIE
Elsevier Global Medical News

Pemetrexed, a folate analog metabolic inhibitor, has been approved as the first maintenance treatment for locally advanced or metastatic nonsquamous non–small cell lung cancer, the Food and Drug Administration announced.

“This drug represents a new approach in the treatment of advanced non–small cell lung cancer,” Dr. Richard Pazdur, director of the FDA’s office of oncology drug products, said in the statement. “Typically, patients whose tumors respond to chemotherapy do not receive further treatment after four to six chemotherapy cycles,” he added.

Dr. Pazdur referred to a study that showed an advantage in overall survival in certain patients who received maintenance therapy with pemetrexed. Maintenance therapy with pemetrexed was compared with placebo in a multicenter study of 463 patients with...
VTE Prevention

ICU * from page 1

Two units, according to Dr. Stein and his colleagues. In the surgical ICU unit, simultaneous physical rounding on every patient is conducted every morning by all members of the frontline clinical team, including the responsible physician. A clinical pharmacist views the real-time relay-and-display program prior to rounds to call attention to appropriateness of VTE prophylaxis during rounds. New VTE prophylaxis orders are discussed and captured via new physician phylaxis orders are discussed prior to rounds. The charge nurse views the relay-and-display program to call attention to patients, with more research is needed to examine sustainability and to clarify the most effective implementations of relay-and-display strategies in hospitals, according to Dr. Stein and his colleagues. The researchers acknowledged that they are employees of Emory University and Emory Healthcare. Dr. Stein also disclosed stock holdings with Ingenious Med Inc. and honoraria from Sanofi.

Maintenance Therapy Approved

Lung Cancer * from page 1

Overall survival was a median of 15.5 months, vs. 10.3 months among those receiving placebo. In stage IIb/IV non–small cell lung cancer, whose disease had not progressed after four cycles of platinum-based chemotherapy. Among those with nonsquamous non-small cell lung cancer treated with pemetrexed (481 patients), overall survival was a median of 15.5 months, vs. 10.3 months among those who received a placebo. In non–small cell lung cancer, progression-free survival was a median of 4.4 months among those on pemetrexed, compared with 1.8 months among those who received a placebo, according to the prescribing information. No benefit was seen among patients with predominantly squamous cell cancer. The drug is not approved for patients with squamous cell non–small cell lung cancer.

Dr. Chandra P. Belani of Penn State Cancer Institute in Hershey, Pa., reported the pemetrexed study findings at this year’s annual meeting of the American Society of Clinical Oncology.

Pemetrexed, marketed as Alimta by Eli Lilly & Co., was approved in September 2008 for treating locally advanced or metastatic nonsquamous non–small cell lung cancer in combination with cisplatin, or after previous chemotherapy. It is administered intravenously. Pemetrexed was approved in 2004 for treating patients with mesothelioma.

To view a video interview with Dr. Belani, go to www.youtube.com/watch?v=sJv5w_FoE.

Dr. W. Michael Alberts, FCCP, comments: The benefit of chemotherapy for stage IV lung cancer beyond 4-6 cycles has been questioned and is not recommended in the most recent edition of the ACCP’s Lung Cancer Guidelines. The new information generated from this multicenter study may result in a change in the recommendations in the third edition of the guidelines.
CDC Updates Guidelines on Antiviral Tx of Influenza

Either oseltamivir or zanamivir is recommended for positive A (H3N2), novel A (H1N1), or B strains.

BY MIRIAM E. TUCKER

Either oseltamivir or zanamivir is recommended for positive A (H3N2), novel A (H1N1), or B strains.

Other information providers should consider includes:
- Recommended neuraminidase inhibitors are licensed for chemoprophylaxis of children aged less than 1 year (oseltamivir) or aged less than 5 years (zanamivir).
- A recent Emergency Use Authorization provides information on use of oseltamivir for children aged less than 1 year. Some experts prefer weight-based dosing for children aged less than 1 year, particularly for very young or premature infants.
- When weight-based dosing is used for chemoprophylaxis in infants aged less than 1 year, those 6 months or older should receive 3.5 mg/kg per dose twice daily, and those aged less than 6 months should receive 3.0 mg/kg per dose twice daily. Rather than vote unanimously on recommendations for chemoprophylaxis—as has been done previously with seasonal influenza—ACIP decided instead to include a short paragraph within the treatment guidelines about chemoprophylaxis that will include the address for the CDC’s H1N1 Web page (www.cdc.gov/H1N1).

Call Issued for Greater TB Screening of immigrants

BY MARY ANN MOON

Overseas screening for tuberculosis plus follow-up soon after arrival in the United States could significantly reduce the number of TB cases among foreign-born people in the United States, according to a report in the New England Journal of Medicine.

This approach “is a relatively high yield intervention for identifying cases of active tuberculosis in U.S.-bound immigrants and refugees,” said Yecai Liu of the Centers for Disease Control and Prevention, Atlanta, and his associates.

The researchers analyzed data from the CDC’s notification system for TB among people entering the country to better understand the epidemiology of the disease in this patient population.

In 2007, foreign-born persons accounted for nearly 58% of the 13,291 new cases of TB in the United States. Their rate of TB was nearly 10 times higher than that of people born in the United States. Furthermore, 27.5% of tuberculosis cases among foreign-born persons are diagnosed within 2 years after the person’s arrival in the United States. More than 2,700,000 immigrants and over 378,000 refugees were screened overseas before coming to the United States in 1999-2005. American embassies and consulates in the countries of origin appoint local physicians to perform the screening. The travelers undergo standard chest radiography, and any who have TB symptoms or whose films suggest the disease have sputum smear screening on 3 consecutive days.

At follow-up, after arrival in the United States, active pulmonary TB was diagnosed in 7% of immigrants and 8% of refugees who had received diagnosis of smear-negative TB overseas. The follow-up also revealed active pulmonary TB in the 1.4% of immigrants and nearly 2% of refugees who were originally diagnosed as having inactive disease overseas.

Most cases diagnosed overseas before moving to the United States occurred among people born in the Philippines, Vietnam, China, Mexico, and India. These five countries also account for the majority of cases of TB diagnosed in foreign-born persons in the United States. Dr. Liu and his colleagues (N. Engl. J. Med. 2009;360:2406-15).

It appears that during the study period, 11%-32% of immigrants and 10%-38% of refugees who had been diagnosed as having TB overseas may not have completed follow-up evaluations once they arrived in the United States. “State and local health departments may improve the rate of follow-up evaluation if they can institute active outreach policies,” they added.

Dr. Mark Metersky, FCCP, comments: It has been known for some time that a large percentage of tuberculosis cases in the United States occur in recent immigrants. How to translate that knowledge into more effective screening and prevention remains the challenge.

Up in Smoke? Toxins Found in Electronic Cigarettes

BY ALICIA AULT

The Food and Drug Administration said that it had determined that electronic cigarettes marketed by two manufacturers—containing carcinogens, varying amounts of nicotine, and impurities such as diethylene glycol.

Since July 2008, the agency has been seizing shipments of the so-called e-cigarettes and analyzing them. It has determined that the e-cigarettes meet the legal definition of a drug and a device, and therefore, are being illegally sold. However, the FDA has not, as of yet, taken any additional action, agency officials said in a briefing with reporters. The agency is considering additional steps, said Michael Levy, division director of the Office of Compliance at the FDA’s Center for Drug Evaluation and Research.

The FDA held the briefing to alert the public to its laboratory findings and express concern that the products may be used by children as a gateway to cigarettes, said Dr. Joshua Sharfstein, principal deputy commissioner.

Powered by a battery, electronic cigarettes vaporize chemicals contained in a cartridge; users inhale the vapor.

The FDA analyzed 19 cartridges made by Smoking Everywhere and NJOY. The agency found detectable levels of tobacco-specific nitrosamines—which are known human carcinogens—in half the samples. Most samples also contained impurities known to be toxic to humans, such as anabase, myosmine, and beta-nicotyline. One cartridge contained 1% diethylene glycol, a toxic component of antifreeze. In another instance, cartridges claiming to have no nicotine had low levels of the substance, and the amount of nicotine per puff varied widely.

Generally, the e-cigarettes are marketed as smoking cessation aids or smoke-free alternatives to cigarettes, said agency officials. The products can be purchased online and at retailers, including shopping malls, where children congregate, said Dr. Jonathan Winickoff, chairman of the American Academy of Pediatrics Tobacco Consortium, who participated in the briefing.

In addition, the cartridges come in flavors such as bubble gum, mint, chocolate, and chocolate chip, Dr. Winickoff noted. Such flavors are particularly appealing to children and novice smokers, he said. “Once you’ve smoked an e-cigarette and are nicotine dependent, the leap to a regular cigarette may not be as great,” said Dr. Winickoff, who added that parents should know that “these aren’t safe products.”

For now, the electronic cigarettes will remain on the market. Sunrise, Fla.-based Smoking Everywhere has sued the FDA, claiming it does not have jurisdiction over its products. The agency has argued that it has the power to regulate e-cigarettes in a manner similar to smoking cessation products.

The FDA was recently granted power to regulate all tobacco products. But Mr. Levy said he did not expect that new law to change how the agency will evaluate electronic cigarettes.
Board Halts Trial of Sildenafil for Sickle Cell Disease

**BY MITCHEL L. ZOLER**

Elsevier Global Medical News

The National Heart, Lung, and Blood Institute on July 7 prematurely stopped a trial testing the drug sildenafil as treatment for pulmonary hypertension in adults with sickle cell disease. The trial halted, announced by the NHLBI online on July 28, occurred because of a 38% serious adverse event rate in patients on sildenafil, compared with an 8% rate in the placebo control group among the first 33 patients who finished the 16-week study. No patients in the study died. The most common adverse effects linked to sildenafil use and triggering the study's end were episodes of severe pain, referred to as sickle cell crisis, which led to hospitalizations.

"The increase in sickle cell medical problems is concern enough for us to stop this clinical trial to protect the safety of our participants," said Dr. Elizabeth G. Nabel, NHLBI director. "We encourage patients with sickle cell disease who are taking sildenafil for pulmonary hypertension to talk with their physicians about the potential risks and benefits of the medication and what actions they should consider, including whether to taper off this medication."

"Sildenafil was a very promising drug because it works for almost every form of pulmonary hypertension, and it has an incredible safety profile. The results were unexpected," said Dr. Mark T. Gladwin, the lead investigator for the study, in an interview. Still unclear until further analyses are done is whether sildenafil had a beneficial effect on pulmonary hypertension and whether a subset of patients tolerated the treatment. Sickle cell crisis is a frequent complication, and the pain is often controlled either by high-dose hydroxyurea or by frequent blood transfusions, said Dr. Gladwin, director of the Vascular Medicine Institute at the University of Pittsburgh. If the drug proves beneficial and if the increased rate of sickle cell crisis is controllable, then the drug might still have a future for this indication. A safe and effective treatment is important because pulmonary hypertension is common in sickle cell disease, affecting 30% of patients, and it boosts mortality 10-fold, he said.

A unanimous decision to stop the study, run at nine U.S. centers and one center in London, came from the trial’s independent data and safety monitoring board. The study, begun in 2007 and had enrolled 74 patients over 19 years of age who had sickle cell disease and mild to severe pulmonary hypertension. Sildenafil is approved for use in patients with pulmonary hypertension without sickle cell disease, where there have been no indications of a safety problem. No treatment has been established as safe and effective for pulmonary hypertension in patients with sickle cell disease.

The study received no funding from Pfizer Inc., which markets sildenafil for treating pulmonary hypertension (Revatio) and for erectile dysfunction (Viagra). Dr. Gladwin said he had no financial relationships to disclose.

**Omega-3 Linked to Increase in Acute Lung Injury Deaths**

**BY ROBERT FINN**

Elsevier Global Medical News

SAN FRANCISCO — A placebo-controlled trial of omega-3 fatty acid food supplements in patients with acute lung injury or acute respiratory distress syndrome was terminated early when an interim analysis showed that mortality was worse in patients taking the supplements.

Within 60 days, 26.0% of the patients taking omega-3 fatty acids had died, compared with 16.3% of the controls, a significant difference, Dr. Michael A. Matthay, FCCP, said at a meeting on critical care medicine sponsored by the University of California, San Francisco.

In addition, the patients taking the omega-3 supplements had significantly fewer ventilator-free days within 28 days (14.6 days, compared with 17.4 days for the control patients) and significantly fewer ICU-free days within 28 days (13.9 days, compared with 16.8 days for the control patients).

"There were some phase II data indicating that maybe omega-3s would be beneficial in these patients," said Dr. Matthay of UCSF. "It’s a sobering result, for sure."

The study was part of a trial called EDEN-Omega (Early vs. Delayed Enteral Feeding and Omega-3 Fatty Acid/Antioxidant Supplementation for Treating People With Acute Lung Injury or Acute Respiratory Distress Syndrome), which was intended to investigate both omega-3 supplementation and early versus delayed enteral feeding. While the Data Safety and Monitoring Board (DSMB) terminated the part of the study involving omega-3 fatty acids after 272 patients had been recruited, the enteral feeding part of the study remains ongoing.

To be included in the trial, patients had to have a P/F (arterial oxygen pressure to fraction of inspired oxygen ratio, or PaO2 to FiO2 ratio) less than 300 mm Hg, bilateral infiltrates, a requirement for positive pressure ventilation via endotracheal tube, and no clinical evidence of left-sided cardiac failure. Patients were excluded for many reasons, including severe liver disease and severe chronic respiratory disease.

Patients were randomized to receive either full-calorie enteral feeding or full-calorie enteral feeding plus twice-daily supplementation with omega-3 fatty acids, gamma linoleic acid, and antioxidants. The supplements were continued for 21 days or until the patient no longer required mechanical ventilation. At the time the study was terminated, the increase in 60-day mortality among patients taking the supplements just reached statistical significance (P = .05). The differences in ventilator-free days and ICU-free days were somewhat more certain, with P values of .03 and .02, respectively.

"One can argue about whether there was enough power here to conclude for sure that [omega-3 fatty acids] was deleterious, but it’s certainly strong in that direction," Dr. Matthay said.

Dr. Matthay stated that he had no conflicts of interest to declare. The study was supported by the National Heart, Lung, and Blood Institute.

**FDA Approves 2009-2010 Seasonal Influenza Vaccine**

**BY MIRIAM E. TUCKER**

Elsevier Global Medical News

The Food and Drug Administration has approved a vaccine for 2009-2010 seasonal influenza in the United States. This seasonal vaccine will not protect against the 2009 H1N1 influenza virus that resulted in the declaration of a pandemic by the World Health Organization on June 11, the Food and Drug Administration (FDA), said in a written statement. The agency is working with manufacturers, international organizations, and other government agencies to facilitate the availability of a safe and effective vaccine against the 2009 H1N1 influenza virus, it said.

Even though the 2009-2010 seasonal influenza vaccine won’t prevent disease from the pandemic virus, Americans who are recommended to receive annual influenza immunization are urged to receive it because it is directed against other influenza strains that are expected to be circulating. "Vaccination is the best protection against influenza and can prevent many illnesses and deaths," the FDA said.

The vaccine is being manufactured under six different brand names by six different companies: Afluria, CSL Ltd.; Fluarix, GlaxoSmithKline Biologicals; Fluvax, ID Biomedical Corp.; Fluorivir, Novartis Vaccines & Diagnostics Ltd.; Fluzone, Sanofi Pasteur Inc.; and FluMist, MedImmune Vaccines Inc. All contain the same three influenza strains, which are predicted to be the predominant circulating strains in the upcoming season: an A/Brisbane/59/2007 (H1N1)-like virus, an A/Brisbane/10/2007 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus.

In particular, the FDA said, vaccination of those at higher risk—older adults, young children, and people with chronic medical conditions—as well as health care personnel is important to protecting the pandemic virus.

"Even if the vaccine and the circulating strains are not an exact match, the vaccine may reduce the severity of the illness or may help prevent influenza-related complications," the FDA said.

More information about influenza vaccination is available from the following Web sites:

- Centers for Disease Control and Prevention Web Page on Seasonal Influenza Resources for Health Professionals: www.cdc.gov/flu/professionals/vaccination.
ZYVOX — proven efficacy in nosocomial pneumonia, due to known or suspected MRSA

ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains) or Streptococcus pneumoniae (including multidrug-resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains), Streptococcus pyogenes, or Streptococcus agalactiae. ZYVOX has not been studied in the treatment of decubitus ulcers.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following directly and indirectly acting sympathomimetic, vasopressor, and dopaminergic agents.

Unless patients are carefully observed for signs and symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoma syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine, or buspirone.

Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-related infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis.

Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.

Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.

CNS seizures have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

*For use in methicillin-resistant Staphylococcus aureus.

References:

Please see brief summary of prescribing information on adjacent page.
The effectiveness of the immediate treatment and thus increase the likelihood that the patient will develop severe disease and become non-infectious. Therefore, early intervention is critical.

In patients with uncontrolled hypertension, discontinuation of therapy may be required. The blood pressure should be monitored closely and the patient should be instructed to follow the recommended regimen. If the blood pressure remains uncontrolled, a further reduction in blood pressure may be necessary. A blood pressure of 140/90 mm Hg or lower is generally recommended for patients with uncontrolled hypertension. In patients with uncontrolled hypertension, the blood pressure should be monitored closely and the patient should be instructed to follow the recommended regimen. If the blood pressure remains uncontrolled, a further reduction in blood pressure may be necessary. A blood pressure of 140/90 mm Hg or lower is generally recommended for patients with uncontrolled hypertension. In patients with uncontrolled hypertension, the blood pressure should be monitored closely and the patient should be instructed to follow the recommended regimen. If the blood pressure remains uncontrolled, a further reduction in blood pressure may be necessary. A blood pressure of 140/90 mm Hg or lower is generally recommended for patients with uncontrolled hypertension.
New report from the Dartmouth Atlas of Health Care finds that, overall, the hospital bed supply per capita contracted from 1996 to 2006, while the numbers of hospital-based employees and registered nurses increased.

The number of staffed acute care beds dropped from 2.82/1,000 U.S. residents in 1996 to 2.46/1,000 in 2006, according to the report. However, there was great regional variation. For example, the Jackson, Miss., area had 4.44 beds/1,000 in 2006, compared with 1.45/1,000 in San Mateo County, Calif.

Not surprisingly, the areas with the most beds also had high numbers of hospital employees.

As long ago as the 1960s, Milton Roemer described the phenomenon that a built bed was a filled bed,” noted the report, which was written by Dr. David C. Goodman, Dr. Elliot S. Fisher, and Kristen K. Bronner. “Numerous studies since then have found that higher bed supply is associated with more hospital use for conditions where outpatient care is a viable alternative. This includes most medical causes of hospitalization.”

Physician supply continued to expand “modestly,” although numbers varied greatly by specialty, the report said. For example, the number of primary care physicians increased 11% over the study period, compared with 51% for infectious disease specialists and a whopping 198% for critical care specialists. Specialties that experienced declines included cardiology (–17%), pulmonology (–18%), and general surgery (–19%).

The authors made several suggestions for managing both hospital capacity and physician workforce growth. To reduce “unwarranted” variations in hospital supply, “Congress could require the Centers for Medicare and Medicaid Services to use its capital payment policies to limit the further growth of hospital capacity in markets that are already overcrowded,” they wrote.

“Although Certificate of Need programs have generally not been effective, strengthening Certificate of Need programs or statewide prospective hospital budgeting processes could be used to more wisely target future hospital growth. Neither of these approaches, however, would help reduce capacity in regions that already have an oversupply.”

To better adjust the physician workforce, “a national workforce commission with representation from the clinical professions, public health, health care purchasers, and patients would provide badly needed analyses and research to better direct funds for health workforce training and for provision of care to the underserved,” the authors suggested.

Another alternative for getting both hospital bed capacity and the physician workforce to the right size would be a more market-oriented approach based on organized systems of care, according to the report. “Consensus is emerging that integrated delivery systems that provide strong clinical support to clinicians and team-based care management for patients offer great promise for improving quality and lowering costs,” the authors wrote.

“Policy makers would need to remove legal barriers to collaboration and provide incentives—such as larger payment updates or subsidies for implementing electronic health records—to providers who were willing to establish real or virtual accountable care systems.”

Under a shared savings model, they concluded, “organized systems would have the appropriate incentives to right-size their hospitals and realign their physician workforces with the needs of the populations they serve.”

I ncreased mortality associated with hypoglycemia among patients with acute myocardial infarction (AMI) was associated with insulin treatment, in a retrospective study of nearly 8,000 patients. The study confirms previous findings that development of hypoglycemia during hospitalization is associated with increased short-term mortality among patients with acute myocardial infarction (AMI).

The rate was confined to patients who became hypoglycemic spontaneously, due to conditions such as shock, sepsis, liver or multiorgan failure, malnutrition, or adrenal dysfunction, whereas hypoglycemia arising after the initiation of insulintreatment was not associated with increased mortality. The research was led by Dr. Mikhail Kosiborod of the Mid-America Heart Institute, Kansas City, Mo.

"Our findings provide some degree of reassurance to clinicians that epidemic hypoglycemia events, which occur in a setting of glucose control with insulin, do not appear to be associated with increased mortality risk... While continuing random glucose levels may not be warranted, these data suggest that hypoglycemia is a marker of severe illness, rather than a direct cause of adverse outcomes," according to Dr. Kosiborod and his associates (JAMA 2009;301:1556-64).

Hypoglycemia-Mortality Link

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The investigation included 7,820 patients hospitalized with AMI who were hyperglycemic (blood glucose of at least 140 mg/dL) on hospital admission. Overall, 482 (6%) of those patients developed hypoglycemia, which was defined as any glucose level of less than 60 mg/dL, and 39% (3,045) were treated with insulin. Patients treated with insulin had a higher likelihood than those who were not to develop hypoglycemia (11.4% vs. 2.9%). The severity of hypoglycemic

Perforomist Inhalation Solution

Table 1 shows adverse reactions from the 12-week, double-blind, placebo-controlled trial where the rate in the PERFOROMIST Inhalation Solution group exceeded the rate in the placebo group. It is noted that 5% of patients with cardiovascular adverse events was 4% for PERFOROMIST Inhalation Solution and 4.4% for placebo. There were no frequently occurring specific cardiovascular adverse events for PERFOROMIST Inhalation Solution (frequency greater than or equal to 1%) and greater than placebo. The rate of COPD exacerbations was 4.1% for PERFOROMIST Inhalation Solution and 7.5% for placebo.

Patients treated with PERFOROMIST Inhalation Solution (20 mcg twice daily) in the 52-week open-label trial did not experience an increase in clinically significant adverse events above the numbers expected based on the medical condition and age of the patients.

Drug Interactions

Asthma-Related Deaths and Exacerbations

The studies were not to develop hypoglycemia (11.4% between 40-90 years old (mean, 64 years old) and had COPD, with a mean FEV1 of 1.33 L. The research was led by Dr. Mikhail Kosiborod of the Mid-America Heart Institute, Kansas City, Mo.

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**Beta-blockers**

Beta-adrenergic receptor antagonists (beta-blockers) and fenoterol may inhibit the effect of such other drugs administered concurrently. Beta-blockers do not block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not be treated with beta-blockers. However, under certain circumstances, e.g., as a prophylactic after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In such situations, cardioselective beta-blockers could be used, although they should be administered with caution.

**Notes on Pregnancy**

Beta-blockers are contraindicated in pregnancy. Use during pregnancy is not recommended, unless the mother requires beta-adrenergic blockage. When required, cardioselective beta-blockers should be used, although they should be administered with caution.

**Use in Specific Populations**

**Pregnancy**

During pregnancy, caution is recommended in the use of PERFOROMIST Inhalation Solution. Cardiac monitoring is recommended in cases of overdose during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Women should be advised to inform their physician if they become pregnant while taking PERFOROMIST Inhalation Solution.**

**Labor and Delivery**

There are no adequate and well-controlled human studies that have investigated the effects of PERFOROMIST Inhalation Solution during labor and delivery.

**Beta-blockers**

Because beta-blockers may potentially interfere with uterine contractility, PERFOROMIST Inhalation Solution should be used during labor only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

In reproductive studies in rats, fenoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because other drugs are excreted in human milk, caution should be used if PERFOROMIST Inhalation Solution is administered to nursing women. These are no well-controlled human studies of the use of PERFOROMIST Inhalation Solution in nursing mothers.

Women should be advised to consult their physician if they are nursing while taking PERFOROMIST Inhalation Solution.

**Pediatric Use**

PERFOROMIST Inhalation Solution is not indicated for use in children. The safety and effectiveness of PERFOROMIST Inhalation Solution in pediatric patients have not been established.

The pharmacokinetics of formoterol fumarate has not been studied in pediatric patients.

**Geriatric Use**

Of the 586 subjects who received PERFOROMIST Inhalation Solution in clinical studies, 284 were 65 years of age or older. Of the 123 subjects who received PERFOROMIST Inhalation Solution in the 12-week safety and efficacy trial (48 weeks of safety and efficacy trial), 69 were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger adults. Other reported clinical experience has not identified differences in responses to the elderly and younger adult patients, but greater sensitivity of some elderly individuals cannot be ruled out.

The pharmacokinetics of PERFOROMIST Inhalation Solution has not been studied in elderly subjects.

**Overdose**

The expected signs and symptoms of overdose of PERFOROMIST Inhalation Solution are those of excessive beta-adrenergic stimulation and/or occurrence of any of the signs and symptoms listed under ADVERSE REACTIONS. Signs and symptoms may include angina, hypertension or hypotension, tachycardia, with some patients with 200 beats/min, arrhythmias, nervousness, headache, tremor, anxiety, muscle cramps, dry mouth, pallor, nausea, delirium, tachypnea, malaise, hypoglycemia, hypokalemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of PERFOROMIST Inhalation Solution.

Treatment of overdose consists of discontinuation of PERFOROMIST Inhalation Solution together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce excessive bronchodilatation. Use of oxygen and other evidence to determine the need for oxygen therapy in cases of overdose is recommended.

The minimum lethal inhalation dose of fenoterol fumarate in rats is 156 mg/kg (approximately 3200 times the maximum recommended daily inhalation dose in humans on a mg/m2 basis). The median lethal dose in mice is 50 mg/kg (approximately 50 mg/kg in males, but not at doses up to 5 mg/kg (AUC exposure approximately 750 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian cysts was increased at doses of 5.0 mg/kg AUC exposure was approximately 27 times human exposure at the maximum recommended daily inhalation dose and above. This finding was not observed in the drinking water study, nor was seen in mice.

The incidence of adenocarcinoma of the mammary gland in female rats was increased at doses of 60 mg/kg AUC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose and above. Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonists drugs.

Formoterol fumarate was not genotoxic in standard tests for bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in human hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and microsomal test systems in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg approximately 100 times the maximum recommended daily inhalation powder dose in human on a mg/m2 basis.

**Animal Pharmacology**

Studies in laboratory animals (mice, rats, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death with histologic evidence of myocardial necrosis when beta-agonists and methyldopa are administered concurrently. The clinical significance of these findings is unknown.

**Drug Interactions, Xenobiotics, Drugs, or Diuretics**

**Patient Counseling Information**

**Alcohol**

PERFOROMIST Inhalation Solution is not indicated for use in patients who have a history of alcohol addiction, have alcoholism, or have a strong desire to drink alcohol. The use of alcohol should be avoided when using PERFOROMIST Inhalation Solution. Alcohol should not be used with PERFOROMIST Inhalation Solution.

**Beta-Adrenergic Antagonists**

Patients who have been taking beta-blockers (e.g., salbutamol) should be instructed not to use more than one beta-agonist medication at a time, because of the risk of severe bronchospasm and death. This combination should only be used in emergency situations.

**Beta-Blockers**

In patients with known diabetes mellitus, the signs and symptoms of overdosage may be associated with significantly higher mortality among patients who were not treated with insulin than in those who did not have hypoglycemia (odds ratio 2.32). However, among those beta-agonists who were treated with insulin, there was no significant relationship between hypoglycemia and mortality (OR 0.92).

The investigators also found that exogenous hypoglycemia was found to be associated with significantly higher mortality among patients who were treated with oral antihyperglycemic agents during hospitalization did not change the study findings, nor did exclusion of those who died within 24 hours of hospital admission. Changing the definition of hypoglycemia to blood glucose levels less than 70 mg/dL also did not alter the findings, and the relationship between hypoglycemia and mortality did not appear to differ between those with and without known diabetes, Dr. Kosiborod and his associates noted.

In an accompanying editorial, Dr. David M. Nathan, said, “While intensive glucose management has been actively promoted in intensive care units for patients with either known diabetes or patients who have become diabetic for the practice has been tempered recently, as several observational studies have suggested that it is associated with hypoglycemia and worse outcomes (JAMA 2009;301:1599-1601).” While the current study “seeks to provide reassurance that the major risk associated with hypoglycemia is in a subgroup of patients with acute myocardial infarction and nonmedication hypoglycemia,” it “does not directly refute the previous concerns, which have now been heightened by the NICE-SUGAR (the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) trial results demonstrating increased mortality in critically ill patients treated with intensive glucose control,” said Dr. Nathan, director of the Diabetes Center at Massachusetts General Hospital, Harvard Medical School, Boston.

The study was funded by the American Heart Association Career Development Award in Implementation Research awarded to the Centers of Excellence for the National Institute of Biomedical Imaging and Bioengineering. Several other researchers disclosed advisory or grant relationships with pharmaceutical companies.

Health Info for Spanish Speakers

The Agency for Healthcare Research and Quality has expanded its Spanish-language health web site for patients. The enhanced site includes a monthly health advice column and more than 35 consumer guides on surgery, quitting smoking, cardiac rehabilitation, prescriptions, health insurance, and quality of care, among other things. The site includes audio spots on diabetes, osteoarthritis, preventive health, and more. Visit the Web site at www.ahrq.gov/consumer/espanol.htm.
Vaccine Refusal Radically Increased Pertussis Risk

**BY MICHELE G. SULLIVAN**
Elsevier Global Medical News

Children whose parents refused the pertussis vaccine were 23 times more likely to contract the disease than children whose parents allowed them to receive the vaccine, a case-control study found.

Of 156 pediatric pertussis cases identified in a large health care database, 18 (12%) had not received the pertussis vaccine because of parental refusal. Of the 595 matched controls, only 3 (0.5%) had parents who refused to have them vaccinated, Jason M. Glanz, Ph.D., and his colleagues reported (Pediatrics 2009;123:1446-51).

The study was conducted in Colorado, a state with generally high rates of childhood immunization, wrote Dr. Glanz of the Kaiser Permanente Colorado Institute for Health Research, Denver. “Despite high pertussis immunization rates in Colorado, herd immunity did not prevent a high relative risk for pertussis in vaccine refusers,” he and his colleagues observed. “This is likely because of a combination of waning immunity to pertussis in adolescents and adults, ongoing endemic circulation, the highly contagious nature of the bacterium, and frequent asymptomatic infections.”

The study offers a sobering look at the results of the growing trend of vaccine refusal, Dr. Randy Bergen said in an interview.

Among children with confirmed disease, 12% had not been vaccinated because of parental refusal, he said.

Dr. Bergen, chair of the pediatric infectious disease section at Kaiser Permanente Northern California, Walnut Creek, said the antivaccine campaigns of several outspoken celebrities continue to influence parental decisions about their children’s health care.

“And not only are these unvaccinated children being put at risk of contracting an infectious disease, they are putting vaccinated children at risk as well,” said Dr. Bergen.

The study examined pertussis vaccination rates and disease prevalence in children aged 2 months to 18 years enrolled in the Kaiser Permanente of Colorado health plan between 1989 and 2007. Each case of pertussis was matched to four randomly selected controls.

Children were considered “vaccine refusers” if their medical charts documented a parental refusal of one or more pertussis immunizations for nonmedical reasons.

The review identified a total of 156 children who had a confirmed diagnosis of pertussis during the study period. Of these, 17 (11%) had parents who refused all the recommended pertussis immunizations; 1 additional child received only one of the recommended doses. Six percent had to be hospitalized for the illness. The mean duration of cough at diagnosis was 12 days.

The cases (mean age, 9 years) were matched with 595 controls, none of whom contracted the disease. Only three of the control children (0.5%) had parents who refused one or more pertussis immunizations. Children who were not vaccinated were 23 times more likely to contract pertussis than were vaccinated children.

Because some of the children in the primary analysis were not Kaiser members during the entire first 20 months of their life, when they would have received all four primary vaccine doses, the investigators conducted a secondary analysis of 27,748 children who were continuously enrolled in the program from 2 to 20 months of age. This cohort included 31 children with confirmed pertussis infections, who were matched with 308 controls. Among the cases, 13% had parents who refused the vaccine; among the controls, only 0.7% had parents who refused.

“The study highlights the need for effective risk communication between parents and physicians about vaccines and the diseases they prevent,” Dr. Glanz and his colleagues wrote.

Dr. Bergen, who is also a practicing pediatrician, agreed, saying that many parents who express concerns about vaccine safety feel more comforted after hearing the scientific evidence of their safety. A second group, however, is tougher to convince.

“These parents are adamant in their mistaken impression that vaccines are dangerous, and they will not be dissuaded by any information about the severity of the infections vaccines prevent, or the lack of any evidence that vaccines cause autism or any other harm.”

Although the physician’s role is to provide sound information backed by strong science, the final decision of whether to vaccinate remains a parental one, he said. But perhaps the issue should also be viewed from a community perspective, Dr. Bergen suggested.

“This study suggests that parents who don’t vaccinate are putting the community at risk, as well as their own children. It’s similar to the secondhand smoke argument. I understand that those parents are entitled to their choice, but why is that choice more important than another parent’s choice to vaccinate? I may not have the right to make the decision for a parent, but I do have the right to have some input about the environment my child is in,” he said.

Dr. Glanz and his associates indicated that they had no conflicts to disclose. Dr. Bergen likewise had no conflicts of interest.

Acetaminophen May Lengthen Asthmatics’ Hospital Stay

**BY KERRI WACHTER**
Elsevier Global Medical News

Baltimore — Acetaminophen use may contribute to prolonged hospital stay and increased cost during asthma exacerbations in children, according to a retrospective study of 662 patients.

The average length of stay for pediatric patients who received acetaminophen while in the hospital for an asthma exacerbation was 77 hours, compared with 56 hours for children who did not receive acetaminophen, Dr. Floroy Nkoy and her colleagues reported in a poster at the annual meeting of the Pediatric Academic Societies.

Similarly, the average cost of hospitalization for children who received acetaminophen was $4,580, compared with $3,201 for those who did not.

The researchers conducted a retrospective cohort study of children aged 2-17 years who were admitted to a tertiary care children’s hospital with a primary diagnosis of asthma. The study period was from January 2004 to December 2006.

Patients were identified through pharmacy data, according to Dr. Nkoy of the division of pediatric inpatient medicine, University of Utah, Salt Lake City, and her colleagues.

A total of 662 children were admitted to the hospital for asthma during the 3-year study period.

Of these, 21.5% received acetaminophen during their hospital stay and met the inclusion criteria. Pediatric patients who had other chronic medical conditions or who received both acetaminophen and ibuprofen were excluded from the study.

The researchers recorded data including acetaminophen prescription, number of doses, hospital length of stay, and costs. Covariates included age, gender, case-mix severity index, body mass index, presence of confirmed viral infection, and presence of an exacerbation. Multivariate linear and logistic regression analyses were performed to determine whether the use of acetaminophen was associated with hospital length of stay, costs, and resource utilization after controlling for covariates.

The relative resource use for acetaminophen versus no acetaminophen was 36.3 vs. 25.5 for patients who received acetaminophen, compared with patients who did not receive acetaminophen during their hospital stay.

Dr. Nkoy did not report whether she had any relevant financial relationships.

Heliox Boosted Response To Bronchiolitis Treatment

**BY MICHELE G. SULLIVAN**
Elsevier Global Medical News

Nashville, Tenn. — Heliox may have a beneficial effect when used to deliver racemic epinephrine to young children with bronchiolitis, according to the results of a randomized controlled trial of almost 70 pediatric patients.

Children treated with a combination of epinephrine and heliox improved significantly more than those treated with epinephrine and oxygen, Dr. In Kim reported in a poster presented at the annual congress of the Society of Critical Care Medicine.

The investigation included a total of 69 children aged 2-12 months, all of whom still had a Modified Wood’s Clinical Asthma Score of at least 3 after an initial treatment of nebulized albuterol.

The investigators randomly assigned the children to receive nebulized racemic epinephrine delivered either by heliox (a mixture of 70% helium and 30% oxygen) or by 100% oxygen using a face mask.

After the nebulization, all patients continued receiving their randomized treatment via a nasal cannula.

After 60 minutes of treatment, children whose bronchiolitis scores were 2 or higher received another dose of the nebulized racemic epinephrine, followed by continued inhalation via nasal cannula.

After a period of 60 minutes, children receiving the epinephrine alone had significantly more improvement than children receiving the drug by oxygen.

The difference was significant early on and continued to grow," Dr. Kim, a pediatric emergency physician at Kosair Children’s Hospital in Louisville, Ky., said in an interview.
Recommend Flu Shots to Asthma Patients

**BY DENISE NAPOLI**
Elcierve Global Medica News

**Baltimore** — Among children with asthma who received a recommendation from their physician to get the influenza vaccine, the rate of subsequent vaccination was 76%, compared with 16% among children who reported not having received a recommendation from their physician.

The low vaccination rate among the children who did not receive a recommendation, therefore, contributed to a relatively low vaccination rate among the entire cohort (57%), for whom the flu shot is strongly recommended.

The data, which were presented in a poster at the annual meeting of the Pediatric Academic Societies, should serve as a reminder to all physicians treating pediatric asthma patients that their guidance really does have a profound effect, according to study author Dr. Kevin J. Dombkowski. Dr. Dombkowski is from the child health evaluation and Research unit in the division of general pediatrics at the University of Michigan, Ann Arbor.

A total of 189 parents of children with asthma were interviewed over the phone between April and June 2008. The children were between ages 5 and 18 years, and were culled from Michigan Medicaid and Title V files.

Parents were asked about health care utilization during the prior 2007-2008 influenza season, as well as vaccination during that season.

Overall, 153 parents, or 81%, had gone to see their physician for asthma management or treatment sometime during the flu season, either as part of a regular checkup or following an acute problem.

“Most [patients] have an office visit at which influenza vaccine could be given,” wrote the authors, or during which a strong recommendation to receive the shot could be communicated.

The data also revealed a lack of education about influenza vaccine among these high-risk children and their parents.

When the 82 parents who reported that their child had not received a flu vaccine were asked why, several of the reasons given included that no one had told them that a flu shot was needed for their child (19%); they thought that their child did not need one (18%); or were concerned that the influenza vaccine would result in their child getting the flu (10%).

Although 70% of patients reported receiving a recommendation from their physician in this study, Dr. Dombkowski said in an interview that physicians can do better.

He referenced a study he conducted several years ago in a different setting, which showed that only 20% of asthmatic patients had received the flu shot.

“Meanwhile, over 60% of these kids [in the study] had been in the office during flu season,” he said, revealing the “missed opportunities” for influenza vaccine education, recommendation, and administration.

Dr. Dombkowski disclosed that the study was funded by the Blue Cross Blue Shield of Michigan Foundation.

**Recent survey reveals patient attitudes regarding nebulization in the treatment of COPD**

KRC Research, in conjunction with the COPD Foundation, recently conducted the Nebulization for Easier Breathing (NEB) Survey to gain an understanding of the general attitudes toward nebulization in the treatment of COPD. There were 800 participants: 400 patients with COPD and 400 caregivers. The NEB Survey was completed March 2009.1

The reality is 89% of patients with COPD are very satisfied with their current nebulizer treatment. In fact, patients claim that using a nebulizer is better than using only an inhaler.

It’s not just those with COPD who favor nebulized therapy—it’s caregivers, too.

Virtually all caregivers believe that nebulization helps their patients breathe easier. But don’t just take their word for it. Here’s the patients’ perspective. Nearly 91% reported being able to breathe easier when using nebulization as part of their therapy. Actually, it’s referred to as the most positive aspect of nebulization therapy.

The benefits of nebulized therapy are truly numerous—patients describe feeling more comfortable in their chests, and also feeling that they have more control over their symptoms. The majority of caregivers reported an equally powerful effect from nebulization.

As a matter of fact, nebulization helps patients feel confident that they are getting the right dose of their medicine. Again, caregivers concur!

Ultimately, patients who are using nebulized therapy as part of their treatment feel that it allows them to be more active—which reverses a stereotype.

Many COPD patients who utilize nebulization can still lead a fulfilling, active life.

When asked whether they agreed with the statement “The overall quality of my life has improved since beginning nebulization,” three-quarters of patients and caregivers agreed. What’s more, patients and caregivers agreed that the benefits of nebulization far outweigh any challenges.

All in all, more than half of the patients surveyed wished that they could have been prescribed nebulized therapy sooner!

You might ask yourself if patients consider their nebulizer device too bulky or cumbersome—and the conclusion is “no!” The majority of patients surveyed—75%—have no complaints!

With the recent NEB Survey results, maybe it’s time to reconsider starting your patients on the road to more active living and feeling better with nebulized therapy.
As physicians, our days are busy with patients’ medical and personal issues. Those of us in private practice are also small business owners, faced with the same management problems as any other small business. Our days are full, and evenings are usually spent with family. Recently, I had the opportunity to testify before a Virginia Legislative Committee on behalf of proponents for a piece of legislation addressing telehealth services in the Commonwealth. The attitude of the legislators and commissioners on the panel reminded me of the often too frequent public perception, fueled by exaggerated press reports, of physicians as mendacious and self-serving.

I could not help but contrast their view of our profession with the generally unappreciated activities of socially committed physicians and volunteers who have shaped and developed The CHEST Foundation, the philanthropic arm of the American College of Chest Physicians, was founded in 1996 under the leadership of then ACCP President Dr. Bart Chernow, Master FCCP, President-Elect Dr. D. Robert McCaffree, Master FCCP, and ACCP Executive VP and CEO Alvin Lever, FCCP(Inf). We were fortunate to employ Marilyn A. Lederer, CPA, as COO of The Foundation. Members of the ACCP have built The Foundation into an organization that embodies the spirit of selfless service to others.

The CHEST Foundation has targeted four areas: smoking cessation and prevention of tobacco addiction, recognizing and promoting humanitarian service, fostering clinical research, and compassion, family-focused end-of-life care. Efforts have been directed toward involving the ACCP membership and forming strategic relationships with public and private sector organizations worldwide.

The honors and awards given by an organization are a highly visible statement of its values, and they help to shape its public profile. In the current climate, it is important to recognize and promote the service of individuals and organizations whose professional and philanthropic activities are making a difference in the lives of patients and in society. The CHEST Foundation offers awards that recognize and support the volunteer service of ACCP members worldwide. The named endowments and awards speak clearly to ACCP values. The Roger C. Bone Advocates in End of Life Care Award was created in 2000 to recognize an ACCP member who demonstrates outstanding leadership in end-of-life care. This award honors the late Roger C. Bone, MD, Master FCCP, who wrote about the ethical and humanitarian issues surrounding end-of-life decisions and stressed the importance of communication among physicians and their patients. The D. Robert McCaffree, MD, Master FCCP, Humanitarian Awards Program highlights the humanitarian projects of individuals around the world. Endowments have been established honor remarkable researchers and mentors in our field, including Forrest Bird, MD; Thomas L. Petty, MD, Master FCCP; and Edward C. Rosenow III, MD, Master FCCP.

As important as it is to honor leaders whose exemplary professional conduct have made them role models to our profession, it is equally important to recognize those whose insight and perseverance have improved our ability to care for our patients. The Distinguished Scholar program provides funding for ACCP members whose projects are judged to be crucial to advance compassionate clinical care. This program provides multiyear research grants to ACCP members, focusing on a specific area of cardiopulmonary and critical care medicine. Since its inception in 1996, The CHEST Foundation has awarded more than $5 million to ACCP members to foster cutting-edge clinical research to provide new treatment options for patients around the world. At this time, we have three programs: Distinguished Scholar in Critical Care Medicine, Distinguished Scholar in Respiratory Health, and Distinguished Scholar in Thrombosis. In addition to this program, The Foundation, in partnership, supports a variety of clinical research endeavors, including:

- Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency.
- The Association of Specialty Professors/CHEST Foundation of the American College of Chest Physicians Geriatric Development Research Award.
- The CHEST Foundation/LUNGevity Foundation Clinical Research Award in Lung Cancer.
- The CHEST Foundation California Chapter Clinical Research/Medical Education Award.
- The CHEST Foundation Clinical Research Award in Women’s Health.

As a society, we recognize the importance of global social consciousness. Following up on an initiative of Dr. Udaya Prakash, Master FCCP, who went to Honduras following a devastating hurricane to offer personal medical assistance, The CHEST Foundation established a pro bono committee, under the leadership of Dr. Paul A. Kvale, FCCP, to deliver medical education and services to developing countries. To date, more than 70 ACCP members have dedicated their time and shared their expertise in Cambodia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama, Poland, Romania, and Vietnam.

Closer to home, the Ambassadors Group of The CHEST Foundation works to make The CHEST Foundation programs accessible to members’ local communities. ACCP members’ families, as well as committed individuals, compose the Ambassadors Group, which is open to anyone with an interest in furthering the goals of The Foundation. The group serves as a leader in educating children on the importance of staying smoke-free and on the value of good lung health.

In our daily practice within our communities, we are familiar with the distress of families whose loved one is stricken by a critical illness. In 2002, The CHEST Foundation developed the Critical Care Family Assistance Program to fulfill the unmet needs of families of critically ill patients in hospital ICUs and to foster communication between the health-care team, patients, and their families.

What does all this have to do with our relationships in the legislative and regulatory environment? We cannot advocate effectively without a visible background of community service. The activities of The CHEST Foundation prove how the ACCP, working together with volunteer leadership and strategic partners, can translate a vision of social responsibility into reality. These activities form a sound basis from which to launch our advocacy efforts. Taken as a whole, they convey a socially responsible image and provide a crucial background for our advocacy efforts.

I encourage you to affirm the importance of these efforts and, thereby, enhance our advocacy position by contributing your time and/or making a financial commitment to raise the awareness of these activities in the public view. It is easy to include the $100 contribution on your dues statement. ACCP dues are among the lowest of any medical professional society, and the value is great. Consider attending the Making a Difference Awards Dinner at the annual CHEST meeting and honoring our awardees. Contributions in honor of any of our notable leaders or activities are always welcome.

Information is always available at www.chestfoundation.org.
ACCP to Host Guidelines International Network Conference

BY SANDRA ZELMAN LEWIS, PHD
Assistant Vice President
Health and Science Policy

The American College of Chest Physicians (ACCP) is honored to have been selected to host the Guidelines International Network (G-I-N) 7th Annual Conference to be convened August 25-28, 2010, at the Downtown Chicago Marriott. This will be the first G-I-N conference ever held in the United States and only the second one in North America. The Guidelines International Network is an international not-for-profit association of organizations and individuals involved in the development and use of clinical practice guidelines. G-I-N seeks to improve the quality of health care by promoting systematic development of clinical practice guidelines and their application into practice through supporting international collaboration. Founded in 2002, G-I-N membership now includes organizations from Africa, North America, South America, Asia, Europe, and Oceania.

The scientific conference will address health-care topics, ranging from bench to bedside. As there are so many US and North American organizations, specialty societies, and companies in the business of evidence-based medicine, this conference is expected to be very well attended, boasting representatives from the following areas, all working toward improved patient care and patient outcomes:

- Evidence generation
- Evidence synthesis
- Guideline development
- Guideline implementation
- Performance measure development
- Quality improvement programs
- Health information technology
- Health-care policy

The goal is to improve patient care processes and health-care outcomes. However, the road from bench to bedside is fraught with challenges and gaps, including both knowledge and communication gaps. This conference will aim to attract those who work in fields all along the continuum of evidence-based medicine, with the aim of helping attendees to learn from and gain a better understanding of the needs and offerings of each other. This conference will have peer-reviewed and graded abstracts with presentations and posters selected based on the quality of the studies and the association with the theme content areas. Several high profile keynote speakers will address the attendees.

Watch for more information on the G-I-N conference, including the December Call for Abstract Submissions, in CHEST Physician and on the ACCP Web site, www.chestnet.org. Address questions to Sandra Zelman Lewis, PhD, or Rachel Gutterman at GIN2010_Chicago@chestnet.org.

ACP/IDSA Joint Statement of Medical Societies Regarding Adult Vaccination by Physicians

The American College of Chest Physicians, as a member of the American College of Physicians’ Council of Subspecialty Societies, has signed onto the ACP/IDSA Joint Statement of Medical Societies Regarding Adult Vaccination by Physicians. The statement calls on subspecialists to keep their patients up-to-date with immunizations, either through vaccination or referral to an appropriate provider.

You may have seen in a recent issue of Annals of Internal Medicine (Ann Intern Med 2009; 150:40-44) the 2008-2009 CDC Advisory Committee on Immunization Practices Adult Immunization Schedule, accompanied by an editorial explaining the schedule. The ACP editorial discusses the relevant revisions to the schedule and excerpts the Joint Statement. Links to the schedule, the ACP editorial, the editorial, and other information are available at www.chestnet.org/vaccinations/index.php.
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ith the support of sanofi-aventis, The CHEST Foundation announced a proposal for research for the American College of Chest Physicians and The CHEST Foundation Grants in Venous Thromboembolism (VTE) in January 2009. Two grants of up to $180,000 each were available to ACCP members with expertise in VTE who proposed an outstanding project that included evidence-base compatible programs and tools to address the current gaps in the management and prophylaxis in VTE. All proposed projects were required to include one or more ACCP learning categories within a panel of four ACCP members, chaired by Dr. Pascal O. Udekwu, FCCP, convened to conduct a comprehensive analysis of the applications received, and select the top candidates. Committee members were Dr. Robert C. Hyzy, FCCP, Dr. James M. O’Brien, FCCP, and Dr. Jonathan Halperin, FCCP. Dr. Udekwu conducted a gap analysis by compiling a literature review to identify recent studies in the study of VTE that reflected specific knowledge or skills needed by clinicians and shared his findings with review committee members.

Fifteen applications were reviewed, from 12 states and 4 countries. Using a detailed grading rubric, the committee selected two ACCP members to receive the grants. The first grant recipient is Dr. Eli A. Aki, MPH, of the Research Foundation of the University of Buffalo, Amherst, NY. His project is “Developing and Pilot Testing a Novel Outcome Performance Measure for the ACCP Recommendations for Prophylaxis and Management of Long-term Anticoagulation.” The first goal in Dr. Aki’s proposal is in clinical care: to involve oncology patients with VTE in shared decision making on the type of long-term anticoagulation. His outcome objective is to increase the percentage of oncology patients with VTE who share decision making in the process. His second goal is in performance measurement: to develop a tool enabling a performance measure for the ACCP recommendation related to the type of long-term anticoagulation used. The outcome objective is to post a VTE prevention tool on the ACCP Web site to be downloaded by members to reduce or eliminate hospital-acquired VTE within their health-care systems. Dr. Aki’s second goal relates to system objective to create a CME-base method for participating members to review primary literature relevant to the VTE protocols they plan to adopt. The third goal is to establish permanence and support self-sustaining programs within each health-care system to eliminate or reduce the incidence of avoidable hospital-acquired VTE using appropriate prophylaxis methods. The third outcome objective is for participating health-care systems to provide a method for measuring the incidence and cost of VTE and to reduce the incidence of avoidable hospital-acquired VTE within VTE guidelines.

The second grant recipient is Dr. Thomas A. Morris, FCCP, from the University of California Medical Center, San Diego, CA. Dr. Morris’ project is “User-Friendly VTE Prophylaxis.” His first goal is related to ease of use: to develop a user-friendly VTE prophylaxis program to prevent the prevention of hospital-acquired VTE that can be applied in a variety of medical centers. The outcome objective is to post a VTE prevention tool on the ACCP Web site that can be downloaded by members to reduce or eliminate hospital-acquired VTE within their health-care systems. Dr. Morris’ second goal related to system objective is in implementation to create a CME-base method for participating members to review primary literature relevant to the VTE protocols they plan to adopt. The third goal is to establish permanence and support self-sustaining programs within each health-care system to eliminate or reduce the incidence of avoidable hospital-acquired VTE using appropriate prophylaxis methods. The third outcome objective is for participating health-care systems to provide a method for measuring the incidence and cost of VTE and to reduce the incidence of avoidable hospital-acquired VTE within VTE guidelines.

Dr. Morris is a member of the American Society of Health-System Pharmacists and the Society of Therapeutics. His proposal was selected among 12 applications received, from seven states and one country. The outcome objective of his project is to develop a tool enabling a performance measure for the ACCP recommendations related to the type of long-term anticoagulation used. The outcome objective is to post a VTE prevention tool on the ACCP Web site to be downloaded by members to reduce or eliminate hospital-acquired VTE within their health-care systems. The second goal is in performance measurement: to develop a tool enabling a performance measure for the ACCP recommendation related to the type of long-term anticoagulation used. The outcome objective is to post a VTE prevention tool on the ACCP Web site to be downloaded by members to reduce or eliminate hospital-acquired VTE within their health-care systems.

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There have been safety concerns about inhaled long-acting beta-agonists (LABAs) (Salmeterol, for example) for at least 16 years. Since 1993, when the results of the Serevent Nationwide Surveillance (SNS) study were reported (Castle et al. BMJ 1993; 306:1034). This was a study of 28,180 asthma patients, recruited by general practitioners in the United Kingdom, who were randomized to regular use of salmeterol or placebo in addition to their other asthma medications for 16 weeks. Although asthma control seemed improved with salmeterol, there were more respiratory and asthma-related deaths in the salmeterol-treated group (0.07% vs 0.02%, p=0.105). The US Food and Drug Administration (FDA) was aware of this possible safety signal, i.e., a causative relationship between LABA use and death, when salmeterol (Serevent® Inhalation Aerosol, GlaxoSmithKline; Research Triangle Park, NC) was approved for use in the United States in 1994.

Consequently, another large safety surveillance study (the Salmeterol Multi-center Asthma Research Trial—SMART) began in 1996, with the specific intent of determining whether salmeterol use in asthma was associated with an increase in respiratory- and asthma-related deaths or life-threatening experiences. Unfortunately, this trial had not been completed when a combination product, fluticasone propionate and salmeterol (Advair Diskus, GlaxoSmithKline; Research Triangle Park, NC) was approved for use in the United States in 2000. SMART was prematurely stopped after enrollment of 26,355 patients in 2003 when a significant increase in respiratory- and asthma-related deaths was observed with salmeterol treatment compared with placebo in an interim analysis (Nelson et al. Chest 2006; 129:15).

Since the publication of the SNS and SMART studies, the FDA has taken steps to alert physicians to the possible relationship between LABA use and death. On August 11, 2003, a boxed warning label was added to both Serevent and Advair describing a possible relationship between asthma-related deaths and LABA use. On July 13, 2005, the FDA convened a meeting of the Pulmonary-Allergy Drugs Advisory Committee to discuss asthma-related deaths and severe exacerbations detected in the SMART and SNS trials and other studies performed with formoterol (Foradil® Aerolizer®; Schering-Plough Corp; SP). Kemblow, NJ, approved for use in 2001).

The FDA posed four questions to a panel of outside consultants. Two of the questions were related to the adequacy of labeling information provided on the safety concerns for salmeterol and formoterol. The consultants were also asked whether salmeterol and formoterol should continue to be marketed in the United States. There was general agreement that LABAs marketing should be allowed to continue, but that black box warnings about the risk of death should be included in all LABA products. The other questions asked for suggestions about further studies to evaluate the risks for salmeterol and formoterol, respectively. Numerous study concepts were proposed. After the advisory committee meeting, the FDA published a public health advisory on November 18, 2005, about the health risks associated with LABAs.

The controversy about LABAs transitioned from adults to children when the FDA convened a meeting of the Pediatric Advisory Committee on November 28, 2007. The FDA had approved use of salmeterol for children in 1998 and the combination salmeterol and fluticasone in 2004. The first question the FDA posed to this panel regarded the adequacy of information provided in the salmeterol label about the risk of asthma deaths in the pediatric population. The second question asked on this occasion was whether inhaled corticosteroids (ICS) might play in mitigating LABA associated risks. The committee suggested various approaches to revising LABA labels in ways that inhaled corticosteroids (ICS) might play in mitigating LABA associated risks. The committee suggested various approaches to revising LABA labels in ways that ICS might play in mitigating LABA associated risks.

The most recent installment of the LABA controversy occurred on December 10-11, 2008, when the FDA convened a combined meeting of the Pulmonary-Allergy Drugs Advisory Committee, the Risk Management Advisory Committee, and the Pediatric Advisory Committee to address the issues of LABA use in asthma (www.fda.gov, accessed May 27, 2009).

As part of this meeting, a large amount of data was presented by pharmaceutical companies representing the individual LABAs and the FDA. There were important differences between the pharmacological and clinical data. The FDA and pediatric data, and, as expected, different conclusions about LABA safety. GSK found that the combination salmeterol and fluticasone drug use was associated with a significant reduction in asthma-related hospitalizations and ED visits in both adults and children. In 17,891 patients who received that treatment, there were no asthma-related deaths. GSK attributed safety concerns with LABA use in asthma to either nonadherence with concomitant ICS use or inappropriate (per clinical guidelines) LABA monotherapy use.

At about the same time as this advisory committee meeting, Bateman and colleagues published a metaanalysis of data from 66 GSK trials involving 20,866 patients with persistent asthma who were treated with fluticasone with or without salmeterol (Ann Intern Med 2008;149:33). They found that combined use of an ICS plus a LABA significantly decreased the risk of severe asthma exacerbations but that there were too few cases of asthma-related deaths or asthma-related severe respiratory failure to assess risks associated with LABA use. AstraZeneca, the marketers of the budesonide/formoterol combination product (Symbicort® Inhalation Aerosol; AstraZeneca; Wilmington, DE), approved for use in 2001, reported no evidence of an increased risk of asthma-related serious adverse events with LABA use. In its database of 6,434 patients treated with the budesonide/formoterol combination, there were no asthma-related deaths or episodes of serious respiratory failure. It was recognized, though, that this database was probably too small to detect a death safety signal.

Novartis, representing the worldwide experience with formoterol, also reported too few asthma-related deaths or episodes of respiratory failure to address the second question asked about the role of LABA use in asthma. Those with LABA use asthma experience with formoterol, also reported no evidence of an increased risk of asthma-related deaths or episodes of serious respiratory failure. However, Novartis did report a significantly increased rate of serious asthma exacerbations in both adults and children with formoterol treatment compared with placebo. Both AstraZeneca and Novartis concluded that the risk to benefit profile of LABAs was favorable.

In contrast, the FDA statistical reviewers provided an overview of 60,954 patients treated in 110 trials with various different LABAs. Using a composite endpoint of asthma-related deaths, intubations, and hospitalizations, this metaanalysis demonstrated a significant increase in these outcomes with LABA use. Two subanalyses provided important clarifying information. The safety risk while using LABA was greatest in the 4- to 11-year old age population. The safety risk when LABA was used with an ICS was not apparent.

Questions posed to the combined committees focused on the use of LABAs as monotherapy, as part of combination therapy with an ICS, and in adults, adolescents, and children. The combined committees strongly endorsed guideline recommendations for asthma therapy and emphasized that asthma monotherapy with LABAs was not appropriate. Further, combination therapy was strongly endorsed for adult and adolescent patients with asthma not controlled with low-to-medium dose ICS but not as clearly for children. Again, the combined committees suggested labeling revisions on products containing LABAs and proposed a variety of study designs to further characterize the LABA risk profile.

A single observation can summarize the situation following this most recent FDA meeting: “Not much had changed since the 2005 meeting of the Pulmonary-Allergy Drugs Advisory Committee, when safety concerns about LABAs had been raised” (Kramer. N Engl J Med 2009; 360:1952). The cynical observer might actually say that not much has changed since the SNS trials results were published in 1993.

The pharmaceutical companies, reviewing their own relatively small databases, believe their products are safe and effective, but with evaluation of larger data-bases, concerns about a serious safety signal with LABA use in asthma appear. The only certainty about this is that appropriately designed studies to answer simple questions still have not been performed after 16 years of the LABA controversy. Does regular use of LABAs in asthma increase the risk of severe asthma-related events, particularly respiratory failure and death? If so, does regular use of an ICS with a LABA reduce this risk? Are there subgroups of asthma patients, such as blacks or children, at increased risk for a LABA-associated severe outcome? If low might LABA use predispose to severe asthma-related events?

Revising the label to alert physicians to a possible safety concern is not a sufficient response to this controversy, because it continues to put clinicians in a frustrating situation. For patients with persistent asthma who are not responding to ICS, they can recommend add-on LABA use which, per guidelines (NAAEP EPR 3, 2007, NIH, 2007, 2009) might be expected to improve asthma control but which the FDA suggests places the patient at increased risk of death.

The comments by Drazen and O’Byrne (N Engl J Med 2009; 360:1671) must be echoed strongly. It is absolutely incumbent on the FDA and the appropriate pharmaceutical companies to design and perform the clinical trials needed to answer questions about the safety concerns of LABAs in asthma in a timely fashion.

**Déjà vu All Over Again: The Ongoing LABA Controversy**

Dr. Gene L. Colice, FCCP
Director of Pulmonary, Critical Care and Respiratory Services
Washington Hospital Center
School of Medicine
Washington, DC

Dr. Colice is a speaker/advisory board member/consultant to Schering-Plough Corp, Novartis, GlaxoSmithKline, Pfizer, Lilly, Dey, Teva, Almirall, Forest, and Genentech.
Low-Molecular-Weight Heparins: Update on Follow-on “Generic” Compounds (Part 2)

The American College of Chest Physicians convened a roundtable discussion in November 2008 with an expert panel to review issues surrounding the scientific and clinical issues integral to the process for the US Food and Drug Administration (FDA) considering and approving follow-on low-molecular-weight compounds. A panel of clinicians who use low-molecular-weight heparins (LMWHs) in daily practice discussed the issues and provided reaction to the presentations. Part 1 of the roundtable proceedings was published in the July 2009 issue of CHEST Physician and summarized the presentations from the meeting.

This article (Part 2) summarizes the reactions of the roundtable participants during the discussion in November 2008 with the presentation of portions of the molecules are not completely understood; these molecular segments may contribute to the immunogenic potential of UFH and, to a lesser extent, of LMWH. The subcutaneous route by which LMWHs are administered may contribute to immunogenicity; this route mimics vaccination and may increase risk for immune reaction.

Whereas the constituents of a chemical drug are well characterized and the manufacturing process transparent, the same cannot be said for the LMWHs. Differences between LMWH drugs may begin with the selection of animal species from which starting material for UFH is obtained and continue through derivation of a LMWH from UFH by unique, proprietary manufacturing processes. These differences may influence drug efficacy and safety. Thus, by US regulatory standards, each LMWH has been considered a distinct pharmacologic agent requiring clinical trials for approval of each requested indication.

The FDA has not had a well-defined regulatory process to accommodate review and approval of drugs of biologic origin such as LMWHs. Only recently has there been a term accepted by the FDA to describe “generic” versions of drugs of biologic origin, such as the LMWHs. The term now accepted for regulatory purposes is “follow-on” drug.

The FDA approved the follow-on human growth hormone Omnitrope® (Sandoz; Princeton, NJ) under Section 505(b)2 of the Food, Drug and Cosmetic Act, relying on earlier approval of the branded innovator product. Omnitrope was characterized as a “follow-on protein product,” which the FDA describes as “a protein or peptide product intended to be sufficiently similar to a product already approved or licensed to permit the applicant to submit an abbreviated process.”

THE HATCH-WAXMAN ACT ALLOWS THE FDA TO APPROVE A GENERIC VERSION OF THE REFERENCE-BRANDED DRUG WITHOUT CLINICAL TRIALS.

The physicochemical characterization of unfractionated heparin (UFH) and LMWH is incomplete. The functions of portions of the molecules are not logically equivalent to the branded drug. The manufacture of a generic drug must provide the FDA with complete information about the generic product to ensure that the generic is pharmaceutically equivalent to the branded product. This information includes complete chemical characterization, pharmacokinetics, pharmacodynamics, and manufacturing and quality control processes. In the case of chemical drugs, the data are expected to demonstrate equivalence.

LMWH Issues in the Regulatory Process

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eventually charged for the follow-on time will add significantly to the cost of funded clinical trials in various patient populations. Why Clinical Trials Are Needed

The following are contentions for not requiring clinical trials for approval of LMWH follow-on drugs.

► Assumed Efficacy and Safety. On the basis of data furnished to the FDA by a manufacturer, and by postmarketing surveillance of the brand-referenced drug, efficacy and safety of a follow-on LMWH drug could be regarded as adequately demonstrated for approval without need for clinical trials. Further postmarketing surveillance of the follow-on drug should be required.

► Regulatory Definition of LMWH. Defining LMWH as a drug different from a chemical drug confuses the regulatory approval process. If a follow-on LMWH drug has anti-factor Xa/Ila activity satisfactorily close to that of the branded product, and satisfactorily meets standards for other assays required by the FDA, approval of the follow-on drug should be permitted.

► Uniformity in Review and Approval. Unfractionated heparin is notable for lack of knowledge about the physiochemical properties of the potentiating molecule; it has been regulated and approved for years under Section 505 of the US Food, Drug, and Cosmetic Act. If this process has been satisfactory, why should LMWHs be treated differently?

Why Clinical Trials Are Needed

The following are contentions for requiring clinical trials as an essential part of the regulatory approval process for follow-on LMWH drugs:

► Each Follow-on LMWH Should Be Treated as a New Drug. LMWHs are different from one another at the molecular level by virtue of different starting materials and proprietary manufacturing processes. UFH, anticoagulant activity is associated with only a portion of the molecule, and the larger portion of the molecule is poorly understood and not well characterized. LMWHs have differing efficacy and safety profiles as demonstrated in clinical trials and in clinical use.

The multiple differences between the LMWHs make them noninterchangeable in clinical use. There should be no expectation that the approval process for chemical generic drugs, which does not require clinical trials, would be adequate to ensure efficacy and safety of follow-on LMWH drugs in all anticipated patient populations. Even if a LMWH manufacturer realizes its proprietary manufacturing process, the end product is still a molecule that is not completely characterized in function. Thus, each follow-on LMWH should be required to follow the application, review, and approval process for a new drug, including clinical trials of adequate population size and duration for each requested indication.

► No Data Can Substitute for Data Derived From Clinical Trials. A completely characterized chemical drug can be reasonably expected to perform the same in clinical use, whether it is a branded drug or a generic version of the branded drug, as long as bioequivalence is comparable. LMWHs are not completely characterized, and there is no adequate assurance that a follow-on drug will be equivalent to the branded drug in every clinically important respect. Clinical history of a reference-branded drug and data provided by a manufacturer are not adequate assurances. Only clinical trials can provide the necessary assurances. The price of not gathering the necessary information in clinical trials is risk for prophylactic and therapeutic failure of the follow-on drugs in clinical practice.

Summary

Considering scientific evidence, clinical experience, health systems concerns, and regulatory review and approval issues, the majority of attendees agreed that clinical trials should be required for FDA approval of follow-on LMWH drugs. Assurance of efficacy and safety of follow-on LMWHs carried the most weight in the panel’s determination that clinical trials should be required.

However, there were several attendees who disagreed that clinical trials are necessary. An argument in opposition to clinical trials was the cost to drug manufacturers and the ultimate cost to the patient using follow-on LMWHs. Raising the cost of a generic product was seen as negating the rationale for generic drugs.

Moreover, UFH is currently classified as a drug, not a biologic, and the generic heparins are all that is available. Dissenting participants were not convinced that clinical trials would be necessary for follow-on LMWHs, provided that a follow-on LMWH has anti-factor Xa/Ila activity satisfactorily close to that of the branded product and provided that it satisfactorily meets standards for other assays required by the FDA.
Monitoring Technology in the ICU: An Iconoclastic View

Dr. Neil Halpern, FCCP
Editor, Critical Care Commentary

Recent multicenter trials (eg, ESCAPE, ARDSnet, PAC-Man) have all failed to demonstrate an improvement in patient outcome associated with PAC use. Several of these investigators suggest a worse outcome when a PAC is used, even in highly competent hands utilizing sophisticated management algorithms. Despite all evidence to the contrary, many leading authorities in critical care medicine still insist that the PAC is an essential component of intensive care medicine (Vincent et al. Crit Care Med 2008; 36:3093). It is unclear how much evidence would be required before an overwhelming majority of intensivists recognize that there is no longer a place or purpose for the PAC in the current ICU environment. How-ever, enthusiasm and funding for further investigation is lacking, so it seems there will be forever more an academic stalemate regarding this issue.

The intensivists’ quest to obtain more data than trend to further condition being met with a new group of devices based on mathematical analysis of the arterial waveform (eg, FloTrac/Vigileo [Edwards Lifesciences; Irvine, CA]; PICCO [Pulsion Medical Systems; Munich, Germany]; and LiDCO [LiDCO, Cambridge, UK]). These devices have generated more excitement and greater market share than any of these devices. These technologies are based on mathematical analysis of the arterial waveform (eg, FloTrac/Vigileo [Edwards Lifesciences; Irvine, CA]; PICCO [Pulsion Medical Systems; Munich, Germany]; and LiDCO [LiDCO, Cambridge, UK]). These devices have generated more excitement and greater market share than any of these devices. These arterial and venous catheters are used to determine the CO by means of a cold fluid bolus injection into the superior vena cava and monitoring of the temperature change in the artery via a modified Stewart-Hamilton equation (ie, transpulmonary thermodilution CO). Physiologic assumptions that rely on the concept that most of the diminution in temperature of the injectate occurs within the pulmonary vascular bed also permit continuous reporting of extravascular lung water, preload (referred to as global end-diastolic volume), and afterload. Rapidly changing hemodynamic conditions may make repeated cold water injections to reliably obtain a properly calibrated CO.

The manufacturer recommends recalibration at least every 8 h. Thus, while this device is considered “noninvasive,” that description is mostly a misnomer. A recent prospective (nonrandomized) multicenter investigation of 331 ICU patients managed with a PAC vs PICCO (Uchino et al. Crit Care 2006; 10:R174) demonstrated no difference in length-of-stay or mortality between the two groups, however, the PICCO group had a greater differentiation of the treatment group have a greater positive fluid response and a reduced length of hospital stay. In conclusion, the good news is that the noninvasive CO technology that relies on factors, heretofore, unknown to physicians, such as khi, skewness, and kurtosis. Most investigations of this device have simply reported the correlation of its reported data with that of other devices, which, for the most part, has been encouraging, except for one recent study suggesting it was not accurate enough to be of utility in patients with cirrhosis (Biancofo et al. Br J Anaesth 2009; 102:47). No outcome study utilizing this device has been reported.

In conclusion, the good news is that intensivists now have a variety of new and less invasive devices that can report data such as CO, as well as newly recognized data, such as arterial pressure and concentration. However, we must guard against the errors we made in the past as exemplified by CVP and PAC monitoring. Prospective investigations emphasizing the impact of these devices have shown major outcome variables (ie, mortality, length of stay) is necessary before their widespread use, not after.

Dr. Andrew Leibowitz
Professor of Anesthesiology and Surgery
Mount Sinai School of Medicine
New York, NY
The purpose of the ACCP CAC is:

- FCCP, the current ACCP CAC chairman.
-tors working with Dr. Anthony Marinelli,
- Medicare reimbursement issues.
- ACCP representatives working for you on
- for RUC, there is the work of your state
- Plummer, FCCP, as the ACCP RVS Update Committee (RUC)
- Peters, FCCP, as the ACCP CPT Advisor, and his alternate, Dr. Burt
- ACCP RVS Update Committee (RUC)
- Advisor, and his alternate, Dr. Burt
- Medicare CAC Update

The ACCP Practice Management Department invites your participa-
tion on the ACCP Contractor Advisory Committee (CAC). In addition
to the important work of Dr. Steve Peters, FCCP as the ACCP CPT Advi-
sor, and Dr. Scott Manaker, FCCP, as the ACCP RVU Update Committee (RUC)
Advisor, and his alternate, Dr. Burt
Leznick, FCCP, and their ATS col-
leagues, Dr. Stephen Hoffmann, FCCP,
for CPT; and Dr. Alan Plummer, FCCP,
for RUC, there is the work of your state
CAC representatives working for you on
Medicare reimbursement issues.
The Practice Management Committee
is the group of physicians and administra-
tors working with Dr. Anthony Marinelli,
FCCP the current ACCP CAC chairman.
The purpose of the ACCP CAC is:
- To provide a formal mechanism for
ACCP pulmonary, critical care, and
sleep physicians in each state to be
informed of, and participate in, the
development of local coverage deci-
sions (LCD) in an advisory capacity;
- To provide a mechanism to discuss
and improve administrative policies that
are within contractor discretion; and
- To provide ACCP members a forum
for information exchange between con-
tractors and physicians.
The ACCP CAC meets quarterly via
conference call and each year face-to-face at CHEST. An agenda is being developed
for the November 2 meeting in San
Diego. We have a West Coast Medicare
Contractor Medical Director attending to
meet with all the pulmonary CAC repre-
sentatives to discuss the CAC process and
issues of interest.

During a recent conference call of the
multisociety Critical Care Workgroup
(CCWG), Dr. Andrew Blouchuk, MBA, Ju-
risdiction #12 CMD for Highmark
Medicare Services, the Medicare Adminis-
trative Contractor (MAC) for Delaware,
Maryland, New Jersey, Pennsylvania, and
Washington, spoke to the group about ed-
ts identified by ACCP CAC that were in-
appropriately denying payment of claims
for appropriately reported and document-
ted procedures performed on the same day
as critical care, 99291, 99292. He said the
now-resolved problem was with a series of
automatic edits that were correct individu-
ally, but when reported in a certain
sequence, caused inappropriate denials.
For claims denied back to October 1, 2007,
Highmark now accepts resubmission of
claims or appeals of these inappropriate
denials, because of the “Good Cause for
Late Filing” provision allowing claims pay-
ments submitted beyond 120 days of the
d denial. For Highmark states, have your
billing staff or third-party biller review
your critical care claims with procedures
back to October 1, 2007. ACCP was
pleased with the expedient way High-
mark responded to its CAC concerns.
Dr. Marinelli is so strongly convinced of
the importance of the work of the ACCP
CAC that he would like to identify an al-
ternate representative for each state who
can assist in this important work of repre-
senting pulmonary members in individual
states on issues that are related to
Medicare coding and reimbursement. It is
important for every ACCP member to
have active representation in this dialogue
with Medicare. There is a job description
of duties on the ACCP Web site, and, in
addition, we have listed the ACCP CAC
representatives by state. Access at
www.chestnet.org/practice/pm/
representatives.php.

Membrane Diffusing Capacity
On October 27, 2008, 16 pulmonary CAC
members met at CHEST representing 12
states (AK, CA, FL, IL, IN, KS, MD,
MN, OH, OR, PA, RI). ACCP’s CAC
representatives discussed the issue
brought forth by Dr. Alan Plummer’s
article in the practice management sec-
tion of CHEST. They noted the inappro-
priate use of CPT 94725 membrane
diffusing capacity by independent diag-
nostic testing facilities (IDTF). The
ACCP and ATS brought the issue to the
attention of Medicare, and some CAC
members brought the issue to the atten-
tion of their MAC or contractor med-
ical directors. The reference in CHEST
and the link to this article is: The
Carbon Monoxide Diffusing Capacity:
Clinical Implications, Coding, and Doc-
www.chestjournal.org/cgi/content/
abstract/134/3/663.

These are just two examples of the
work of the ACCP CAC. We invite you
to review the ACCP Web site and to
consider working in this important
capacity. We have been unable to iden-
tify CAC representatives in these states:
Colorado, Idaho, Missouri, North Car-
olina, North Dakota, and Wyoming.
Currently, there are only 20 alternate
slots filled. We would like to fill all of
them.

Questions can be addressed to Marla
Brichta at mbrichta@chestnet.org.
Tobacco Regulation, On-Screen Use of Tobacco

**NetWorks**

**Occupational and Environmental Health**

**Enforcing New Laws: FDA to Regulate Nicotine and Tobacco Products**

On June 22, 2009, President Obama signed The Family Smoking Prevention and Tobacco Control Act. This law allows regulation of tobacco products through the US Food and Drug Administration (FDA). A new Center for Tobacco Products will be created within the FDA to establish tobacco product standards. However, the Secretary of Health and Human Services will not be allowed to ban existing tobacco products or reduce nicotine levels to zero. The FDA will use a new standard “as appropriate for the protection of the public health,” to regulate tobacco products.

These regulations are predicted to cut down the number of youth smokers by 11% and adult smokers by about 2% by the year 2019. Moreover, considering recent evidence that shows the strongest negative factor affecting survival in patients with lung cancer (Videtic et al. J Clin Oncol 003(15):1544).

New role of the FDA in the regulation of tobacco and tobacco products can significantly reduce the burden of disease in current and future lung cancers.

Dr. Daya Upadhyay

**Steering Committee Member**

**Private Practice**

**Pulmonary Medicare Contractor Advisory Committee (CAC) Update**

The ACCP Private Practice Network, in collaboration with the Practice Management Department, invites your participation on the ACCP Contractor Advisory Committee (CAC).

The ACCP CAC meets quarterly via conference call and each year face-to-face at CHEST. We invite you to review the information available on the ACCP Web site at www.chestnet.org/practice/pm/responsibilities.php and consider working in this important capacity. ACCP CAC representatives in Colorado, Idaho, Missouri, North Carolina, North Dakota, and Wyoming, as well as alternates for many states are needed.

We would like to identify an alternate representative for each state who can assist in the work related to Medicare coding and reimbursement. It is important for every ACCP member to have active representation in this dialogue with Medicare. A job description of duties and a list of ACCP CAC representatives are available on the ACCP Web site.

Dr. Anthony Marello, FCCP, Chair, ACCP CAC; and Diane Kriet-Morrow, MBA, MPH, CCS-P, ACCP Consultant

**Women’s Health**

The on-screen use of tobacco in Hollywood films poses one of the greatest threats to the long-term health of children. Imagery in movies is a major factor in adolescent smoking initiation. The AMA Alliance Screen Out! is a public awareness campaign to get tobacco out of youth-rated films. The Alliance Screen Out! campaign is working to alter the ratings system controlled by the Motion Picture Association of America (MPAA) so that new movies containing the act of smoking or tobacco products will be rated “R.” It is estimated that this simple change would save up to 120,000 lives and prevent up to one-third of all new teen smokers from initiating smoking. Other initiatives to get tobacco out of youth-rated films include: certify no pay-offs or benefits from having tobacco in the film, require strong antismoking ads, and stop identifying tobacco brands in movies.

Areas of mutual interest and benefit allow for collaboration of the AMA Alliance, The CHEST Foundation, and the Ambassadors Group. The Foundation has developed Lung Lessons™, A Presenter’s Guide DVD to encourage the presentation of important tobacco prevention information to elementary-aged schoolchildren. The Children’s Health Network (WHN), supported by The CHEST Foundation, developed a tobacco prevention speaker’s kit, Make the Choice: Tobacco or Health? The WHN endorses the collaboration of the Ambassadors Group and The Foundation with the AMA Alliance Screen Out! campaign. Collaboration plans between The Foundation and the AMA Alliance include the exchange of Web site links. The Alliance will post a link to “Lung Lessons™,” and The Foundation will post links to Screenout.org and Amastar.org.

Other potential collaborations include promoting each other’s conferences and annual meetings, jointly sponsored workshops, and exploring other mutually beneficial opportunities.

Dr. Sheila Goodnight-White, FCCP

**NetWork Vice-Chair**

**COPD: What Really Works?**

**A Best Practices Workshop for Primary Care**

Attend this intensive 1-day hands-on workshop, and learn the practical skills to identify and treat patients at risk for COPD.

Topics include:

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- Proper Metered-Dose Inhaler Techniques

Benefit from a variety of learning environments:

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**Who should attend?**

Nurse Practitioners • Physician Assistants • Family Medicine Physicians • Internal Medicine Physicians

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March 4, 2010
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August 21, 2010
Peaceful, CT
November 13, 2010
Sarasota, CA

October 22, 2009
San Antonio, TX
March 20, 2010
Memphis, TN
June 26, 2010
Portland, OR
September 11, 2010
Pittsburgh, PA

January 9, 2010
Phoenix, AZ
April 18, 2010
Shreveport, LA
July 10, 2010
Boulder, CO
September 25, 2010
Kansas City, MO

January 23, 2010
Las Vegas, NV
April 24, 2010
Atlanta, GA
July 24, 2010
Raleigh-Durham, NC
October 2, 2010
Louisville, KY

February 26, 2010
Miami, FL
May 22, 2010
Richmond, VA
August 7, 2010
Pocahontas, VA
November 13, 2010
Sarasota, CA

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**This Month in CHEST: Editor’s Picks**

**By Dr. Richard S. Irwin, FCCP**

Editor in Chief, CHEST

- A Randomized Controlled Trial of Standard vs Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in Patients With Suspected Sarcoïdosis. By Dr. A. Tremblay, et al.
- Contamination of Portable Radiograph Equipment With Resistant Bacteria in the ICU. By Dr. P. D. Levin, et al.
- Emergence of New Forms of Totally Drug-Resistant TB Bacilli: Super Extensively Drug-Resistant TB or Totally Drug-Resistant Strains in Iran. By Dr. A. Akbar Velayati, et al.

**Editorials**

- The Mounting Evidence for Endobronchial Ultrasound. By Dr. G. A. Silvestri, FCCP.
- Improving the Standard of Care for Patients With Idiopathic Pulmonary Fibrosis Requires Participation in Clinical Trials. By Dr. D. R. Sraer, on behalf of the IPNet.

**Special Feature**

- A History of Tuberculosis on Stamps. By Dr. M. A. Shampo, and Dr. E. C. Rasenow III, Master FCCP.

**Commentary**


To find details on CHEST’s rising Impact Factor and recognition for excellence in publishing, go to the ACCP Web site: www.chestnet.org. View CHEST online at www.chestjournal.org.
### Significant Redesign of CHEST 2009 Exhibit Hall to a Clinical Resource Center

Don’t miss the all-new Clinical Resource Center, formerly the exhibit hall, redesigned to offer a richer, more valuable educational experience.

The ACCP is making significant changes to transform its traditional exhibit hall into a Clinical Resource Center, where you can complement your learning and find tools and information to advance your practice.

**Experience ACCP**
Your first point of contact in the Clinical Resource Center will be Experience ACCP. Dubbed the nerve center of CHEST 2009, Experience ACCP will feature resources to put everything you learn during education sessions into action.

- Presentations will showcase clinical resources and innovations in chest medicine.
- Experts will be on-hand to engage in conversation.
- New products and exciting initiatives from the ACCP will be displayed.

**Relevant Education**
After passing through Experience ACCP, you will move into the actual Clinical Resource Center for additional learning opportunities. The ACCP is working closely with industry representatives to develop exhibits that offer valuable information and education experiences. Exhibitors have been requested to focus on your learning needs and showcase the clinical value of their products and services. Many exhibitors are expected to offer interactive or hands-on education opportunities.

**Better Layout and Better Hours**
Exhibits in the center will be arranged by specialty clusters, so you can quickly find the areas of focus that interest you. All exhibits relevant to a specialty will be in the same vicinity, so you can easily take in all the resources related to your interests. In addition, the hours of the Clinical Resource Center have been extended, opening 30 minutes earlier each morning and staying open 10 minutes later on Monday and Tuesday, November 2 and 3. More unopposed time is available during center hours, so you won’t risk missing important sessions.

**Favorite Traditions**
Popular features from the traditional exhibit hall will return to the Clinical Resource Center.

As always, you can:
- Have a free lunch. Look for specially marked ‘Have Lunch With the Experts’ areas or luncheon roundtable discussions on practice management issues.
- Play Disease-State Bingo. Visit booths and collect Bingo letters to become eligible to win the prize of the day.
- View original investigation posters. Hundreds of posters will be on display, with unopposed time available during two Poster Grand Rounds and Dessert Receptions.
- Discover new technology at the ACCP-HIMSS Health IT Showcase. Visit this interactive showcase to learn how health information technology can advance your practice.
- Stay connected in the Cyber Café. Use a bank of computers to access the Internet or check your Web-based e-mail.

The all-new Clinical Resource Center will be open Monday, November 2, through Wednesday, November 4. Stop by to experience the revolutionary redesign into a center where clinical resources come first.

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### Ambassadors Program Is Back for CHEST 2009

"Celebrating Our Diversity," an exciting new program that debuted at CHEST 2008, sponsored by The CHEST Foundation’s Ambassadors Group, Anita Mathur, an active member of the Ambassadors Group, gave an insightful multimedia presentation highlighting the different regions and cultures of India.

Upon entering the room, one was filled with the sights and sounds of India. Attendees were greeted by Anita Mathur, Pratima Mathur, and Sabiha Raof, dressed in beautiful saris, the traditional attire for women living in India. They also displayed the common male attire of the dhoti and kurta.

After the presentation, everyone had the opportunity to learn how to wear a sari and receive a copy of some of the Mathur family’s favorite Indian recipes. The Ambassadors Group members encourage you to join them during CHEST 2009 as they continue this delightful and educational series celebrating the diverse cultural heritages of our international Ambassadors. Lorraine Sinclair will give a presentation on the sites, foods, ethnic dress, and traditions of Panama. All are invited to attend this popular Ambassadors Group event that is held in the Ambassadors Group Hospitality and Information Room on Tuesday, November 3, from 3:00 to 4:00 PM.

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### CHEST 2009: Conventional Dining

When hunger strikes at CHEST 2009 in San Diego, you’ll find plenty of flavors to savor—many within walking distance of the San Diego Convention Center. Consider these top picks from the San Diego Convention & Visitors Bureau, all near the convention center.

- **Athens Market Taverna.** A longtime favorite of local business folks, this taverna ranks as one of San Diego’s best Greek restaurants. Best bets include lamb chops and leg of lamb, lentil or lemon-chicken soup, moussaka, and garlicky Greek-style meatballs. Sundays are reserved for private parties.
- **Chive.** Don’t let the minimalist décor fool you—Chive is a great place to indulge the senses. Along with an impressive list of cocktails and wines, look for fresh fish, duck, beef, pork, vegetarian dishes, and desserts worth a trip in themselves. Dinner only.
- **Dobson’s.** A smart, business crowd frequents this bar and grill for topnotch food and people watching. In addition to tables in the bar area, there’s an upstairs dining room that overlooks the scene below. Signature dishes are mussel bisque, veal sweetbreads, lamb, and fresh fish specials.
- **Lou & Mickey’s.** This handsome restaurant and cocktail lounge is a favorite with the meat and potatoes crowd. The menu is heavy on steaks, chops, and fresh seafood but also offers pastas, salads, and lots of appetizers in a friendly, upscale atmosphere.
- **Monsoon Fine Cuisine of India.** Well-prepared Indian food, including vegetarian dishes, are served at this lushly decorated dining room and bar. Highlights of the menu include chicken tikka masala, and fragrant curries and stews prepared from lamb, chicken, or seafood; chicken tandoori; and excellent Indian breads. Sidewalk seating is available.
- **Sally’s.** This restaurant on the boardwalk has some of the best views in town from outdoor tables and seats in the bar. A ‘chef’s table’ in the kitchen can be reserved for up to 12 diners. Specialties include fresh oysters, crab cakes, and fresh fish daily specials.
- **The Yard House.** This fun-loving beer bar and restaurant offers more than 120 varieties of brew on tap and a crowd-pleasing menu. Standouts are the seared ahi, individual pizzas, grilled fresh fish, and mouth-watering burgers.

At the end of the day, you may take a short walk to the convention center and explore San Diego on your quest for a meal. From modest take-out to four-star dining with fabulous views, you can easily find something to suit your tastes. Check out more top picks from the San Diego Convention & Visitors Bureau at http://bit.ly/CHESTdine.

CHEST 2009 is October 31 – November 5. Early registration discounts are available through August 31. Register today and save on the year’s best learning opportunity in clinical chest medicine at www.chestnet.org.
Keeping Tabs on New Palliative Care Meds

BY PATRICIE WENDLING
Elsevier Global Medical News

AUSTIN, TX. — Many new medications relevant to palliative care have come on the market recently or are about to, hospital pharmacist Mary Lynn McPherson, Pharm.D., said at the American Academy of Hospice and Palliative Medicine annual meeting. Dr. McPherson described new prescription drugs and over-the-counter therapies that may often be given to patients at the end of life.

She commented on the following products:

- **Dexlansoprazole (Kapides):** Delayed-release capsules were approved in late January for the treatment of heartburn associated with gastroesophageal reflux disease. This R-isomer of lansoprazole (Prevacid) comes to market just as Prevacid is expected to go generic. Dexlansoprazole is the first proton pump inhibitor (PPI) with a dual delayed-release formulation, allowing doses of $0.60 mg a day, versus 15-30 mg a day for Prevacid. Costs per month are $150 for dexlansoprazole and $168 for Prevacid.

  "We get the patient frequently in my practice in a hospice on a PPI they don’t even need that’s been advertised to death," said Dr. McPherson, a professor of pharmacy at the University of Maryland, Baltimore. "You know, the purple pill, [but] it doesn’t work any better than the 80 cents a day over-the-counter (OTC) omeprazole [Prilosec]. We only provide a PPI if the patient is on a steroid or non-steroidal that we are also providing."

- **Sanacea:** a transdermal patch designed to deliver 3.1 mg of granisetron over 24 hours to prevent emesis caused by emetogenic drugs. Approved by the Food and Drug Administration last fall, the patch is applied to the upper arm at least 24 hours before the first chemotherapy session and can be worn for up to 7 days. In clinical trials, it showed the same efficacy as 2 mg of oral granisetron per day, said Dr. McPherson. Cost is $287 per patch.

The patch may be a better option for inpatient palliative care than for home-based hospice, where Halol (haloperidol) is the mainstay for nausea, she said.

- **Zolpidem (Zolpimist):** 5-mg and 10-mg oral spray was approved in late 2008 for the short-term treatment of difficulties getting to sleep. The spray acts quickly, reaching therapeutic levels in the body in 15 minutes.

- **Tramadol:** is under review by the Drug Enforcement Administration and is expected to be a scheduled drug.

  "Tramadol is not a controlled substance at the federal level, but it may be heading that way," said Dr. McPherson. Arkansas and Kentucky have made it a schedule IV drug, and authorities in North Dakota, Wyoming, and Ohio are tracking tramadol usage through their prescription drug monitoring program as if it were controlled.

- **Propoxyphene:** may be on the chopping block after two FDA advisory committees narrowly voted on Jan. 30 to recommend discontinued marketing of Darvon and Darvocet. Last month, the FDA required the drug’s labeling to include stronger warnings about the risks of overdoses. Propoxyphene is banned in the United Kingdom, but is one of the 25 most prescribed drugs in the United States, Dr. McPherson said. It causes less stomach upset than other opioids.

Both the drug and its metabolite are cardiotoxic. Propoxyphene was a factor in 5.6% of drug-related deaths in the United States from 1981 to 1999, she said.

- **OTC products:** Emuprofen is a topically administered analgesic that contains ibuprofen and oil from the fat of the emu. It is marketed as an anti-inflammatory and an alternative to systemic NSAID therapy for various painful conditions. Cost is about $35 for a small jar. The cream is about 10% ibuprofen.

Rain Dry Mouth Spray may be an option for xerostomia, which is common in people with head and neck cancer. The active ingredient is xylitol, which can raise blood glucose if overused. Cost is $11-$14 for 4.5 ounces.

Tums QuickPak is a powder that dissolves instantly on the tongue without the need for water and is the equivalent of two regular-strength Tums. It can be used not only as a daily calcium source but also for patients who need cytoprotection and can no longer swallow, she said.

Dr. McPherson disclosed that she is a consultant for Alpharma Inc.

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San Diego — The prevalence of headache disorders in patients referred to a sleep lab for sleep-disordered breathing was 70% and consisted primarily of morning headache, a study of more than 200 patients showed.

A relationship between headache disorders and sleep disorder has been described anecdotally in the medical literature for several decades, but this marks the largest-known prospective study to evaluate the association, Dr. Timothy M. Quast reported during a poster session at an international conference of the American Thoracic Society.

“Very few studies have been done on this topic,” said Dr. Quast of the Walter Reed Army Medical Center, Washington. “The ones that we did find were small, of 50-80 patients.”

Dr. Quast and his associates asked 219 consecutive patients undergoing an overnight polysomnography for diagnostic purposes to complete a brief questionnaire to evaluate whether or not headache disorders were present. Respondents affected by headache disorders were asked to complete a more detailed questionnaire to diagnose and characterize the condition.

After all patients underwent polysomnography, the researchers conducted follow-up phone calls at 1- and 3-month intervals to evaluate compliance with their continuous positive airway pressure (CPAP) machine and the effect of CPAP on a comorbid headache disorder.

The mean age of the 219 patients was 44 years, their mean body mass index was 30.4 kg/m², and 66% were male. A total of 154 patients (71%) had a headache disorder present, and 65 did not. Morning headache was most common type of headache disorder (55%), followed by tension headache (49%), migraine headache (32%), and chronic daily headache (16%).

No polysomnography features were predictive of headache disorder, a finding that surprised Dr. Quast. “The patients who had headaches had better sleep indices,” he said. “They had less respiratory disturbances, woke up less frequently, and had fewer hypopneas or apneas. … And they actually had higher mean oxygen saturation levels.”

The researchers also found that CPAP therapy appeared to improve headache symptoms among patients who were compliant with their CPAP machines. “This is another reason that patients need to be compliant with their CPAP,” he commented.

Patients with a headache disorder tended to be younger than their counterparts without the disorder. They also were more depressed and more tired, based on responses to the Patient Health Questionnaire-9 and the Epworth Sleepiness Scale, respectively. “There’s something breaking out here, but we did not have the power to determine what makes these subpopulations different from one another,” Dr. Quast said.

He estimated that a study of at least 500 patients will be required to further elucidate the findings.

Dr. Quast had no conflicts to disclose.

Morning Headache Common in Sleep Disorders

Sleep Apnea May Independently Point to Type 2 Diabetes

Seattle — The risk of type 2 diabetes increased with the severity of obstructive sleep apnea, even after obesity was taken into account, researchers reported at the annual meeting of the Associated Professional Sleep Societies.

Dr. Sonia Togeiro and her colleagues conducted a population-based study of OSA and diabetes among 1,042 men and women aged 20-80 years living in São Paulo, Brazil.

All study participants underwent full-night polysomnography and were classified according to their apnea-hypopnea index as having no OSA (index less than 5), mild OSA (index 5-15), or moderate or severe OSA (index greater than 15).

Participants were defined as having type 2 diabetes if they had a fasting plasma glucose level of 126 mg/dL or higher, took antidiabetic medication, or reported a previous diagnosis of the disease.

Study results indicated that 62% of participants did not have OSA, whereas 21% had mild OSA, and 17% had moderate or severe OSA, reported Dr. Togeiro, an endocrinologist at Federal University of São Paulo. A total of 7% overall had diabetes. In addition, 38% were overweight, and 21% were obese.

Compared with their counterparts who did not have OSA, participants with mild OSA and participants with moderate or severe OSA alike were older (mean age 17 years vs. 48 years and 53 years, respectively), had a higher body mass index (25 kg/m² vs. 28 and 30 kg/m²), and were more likely to have diabetes (3% vs. 9% and 21%).

The presence and severity of OSA were also associated with a more unfavorable metabolic profile, noted Dr. Togeiro. Both OSA groups had higher levels of total cholesterol, triglycerides, fasting glucose, and fasting insulin, and a higher homeostasis model assessment index, compared with the unaffected group.

In a multivariate analysis adjusted for age, sex, and body mass index, participants with moderate or severe OSA had a nonsignificant increase in the risk of diabetes relative to their counterparts who did not have OSA (odds ratio 1.07), and participants with moderate or severe OSA had a significant near doubling of the risk (odds ratio 1.97).

Dr. Togeiro reported that she had no conflicts of interest in association with the study.

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