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COURTESY TERRY L. ROBESON

Real-time relay of VTE prophylaxis order status could work for other hospitals with electronic clinical data, said Dr. Jason Stein.

Automated Data in ICU Boost VTE Prophylaxis

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — Automated real-time relay of the venous thromboembolism prophylaxis order status of all patients at a 550-bed tertiary care teaching hospital significantly increased prophylaxis usage across the ICU, medical, and surgical units.

For at least 5 months after the intervention, 15 nursing units averaged greater than 90% prevalence of venous thromboembolism (VTE) prophylaxis, a level reached by just 5 units prior to the intervention, Dr. Jason Stein and his colleagues at Emory University, Atlanta, reported in a poster at the annual meeting of the Society of Hospital Medicine.

"Real-time relay-and-display may represent a transferable quality strategy for hospitals with electronic clinical data," the researchers wrote.

Pulmonary embolism resulting from VTE is the most common preventable cause of hospital death.

Yet a large U.S. multicenter prospective registry study showed that the majority of hospitalized patients with risk factors for deep-vein thrombosis did not receive prophylaxis (Am. J. Cardiol. 2004;93: 259-62).

In the current study, pharmacologic VTE prophylaxis in the surgical ICU unit significantly increased from 78% at baseline to 94% after the intervention.

That occurred without a significant rise in lone mechanical prophylaxis, which increased from 17.3% to 19.6%.

In a medical nursing unit, the intervention resulted in a significant increase in overall VTE prophylaxis (from 85% to 91%) that was almost entirely attributable to a significant increase in lone mechanical prophylaxis (from 14.6% to 20.2%).

Frontline processes, such as rounding format or timing of capture of new orders, may modulate the effect of the program, and thus explain the different outcomes between the

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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

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Lung Cancer Maintenance Tx Approved

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

Pemetrexed, a folate analogue 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 663 patients with

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Flu Vaccination Priorities

H1N1 • *from page 1*

too young to be vaccinated but are at high risk for influenza-related complications.

► **Group 3–Health care personnel and emergency medical personnel** (such as emergency medical technicians, firefighters, and others whose jobs involve routinely providing emergency medical care in communities). These individuals are seen as a potential source of infection for vulnerable patients. In addition, increased absenteeism could reduce the health care capacity.

► **Group 4–Children and adults from 6 months through 24 years of age.** Children have the highest incidence of illness, and "explosive" outbreaks in schools have been a prominent feature of the spring 2009 epidemiology of the novel H1N1. Children younger than 5 years of age are at the highest risk for hospitalization, and are sources of infection for the community and in schools. Moreover, illness in children keeps parents home from work. Young adults also have high attack rates and are seen as vectors.

► **Group 5–Adults aged 25-64 years with certain medical conditions that place them at greater risk for influenza-related complications.** These include chronic pulmonary, cardiovascular, renal, hepatic, cognitive, neuromuscular, hematologic, and metabolic disorders, as well as immunosuppression caused by medications or HIV infection. About 70% of adults hospitalized thus far with novel H1N1 infections had one of these conditions.

If vaccine demand exceeds availability, subgroups of the larger group, totaling 42 million people, should receive priority. The first subgroups—pregnant women and household and caregiver contacts for infants younger than 6 months of age—remain unchanged as a priority. The next subgroups include health care and emergency personnel in direct contact with patients; children aged 6 months through 4 years of age; and children with chronic medical conditions.

When vaccine availability is sufficient at the local level to routinely vaccinate initial target populations, a decision should be made in cooperation with state and local health authorities to vaccinate healthy adults aged 25-64 years first, then individuals aged 65 years and older. The last recommendation, in contrast to seasonal influenza vaccination recommendations, reflects the fact that older individuals thus far have been at lower risk for the novel H1N1 virus.

New recommendations were needed, Dr. Fiore said, because the federal government's 2007 pandemic vaccine priority guidance had been developed for the scenario of a severe pandemic with the potential for social disruption of critical infrastructure. The ACIP's Influenza Working Group concluded that current epidemiologic and immunologic evidence, combined with updated information on vaccine supply and availability timelines, indicated a need to revise recommendations that had been made during prepandemic planning. ■

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 orders during rounds.

In contrast, the rounding format in the medical unit is asynchronous physical rounding on patients by clinical team members. A multidisciplinary team meets on weekday mornings to discuss individual patients.

The charge nurse views the relay-and-display program to call attention to patients, with no order for VTE prophylaxis during the team meeting.

New orders are discussed but not captured during the meeting, and the nurse follows up ad hoc.

"More research is needed to examine sustainability and to clarify features of 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*

stage IIIb/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 this group, progression-free survival was a median of 4.4 months among those on pemetrexed, compared with 1.8 months among those on 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.

Overall survival was a median of 15.5 months, vs. 10.3 months among those receiving placebo.

DR. BELANI

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=9S_-jhW_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.*

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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
Elsevier Global Medical News

ATLANTA — The Centers for Disease Control and Prevention's vaccine advisory panel voted to update its guidelines on antiviral treatment of influenza to include new information about antiviral resistance of seasonal influenza and address influenza caused by the newly emerging pandemic strain of H1N1.

At the time of the Advisory Committee on Immunization Practice's June meeting, all pandemic H1N1 viruses tested were sensitive to oseltamivir and zanamivir and resistant to adamantadines. In contrast, seasonal H1N1 influenza is resistant to oseltamivir but susceptible to the other two antivirals. As of now, all circulating seasonal influenza H3N2 and B strains are susceptible to zanamivir, Dr. Anthony J. Fiore of the CDC's Influenza Division said at the meeting.

Subsequent to the meeting, a patient with oseltamivir-resistant novel H1N1 was identified in Denmark. This does not change the recommendations the committee voted on, CDC spokesman Tom Skinner said in a interview.

Antiviral treatment should be started as soon as possible after illness onset. Persons for whom antiviral treatment should be considered include those with influenza viral pneumonia or influenza and complicating bacterial pneumonia. The treatment also should be considered for patients hospitalized with influenza and those at higher risk for influenza complications, regardless of illness severity.

Zanamivir is recommended if laboratory testing is not done or is negative but there is clinical suspicion of influenza. The antiviral also is recommended if a patient tests positive for influenza A, influenza A and B, or seasonal A (H1N1).

Combined treatment with oseltamivir plus rimantadine is an acceptable alternative if zanamivir is unavailable or can't be tolerated.

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 not 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 simultaneously 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).

Information on that site is updated frequently, and the need for chemoprophylaxis is expected to change as more becomes known about transmission of the novel H1N1 virus and vaccine availability, ACIP member Dr. Kathleen Neuzil said in an interview. ■

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Seasonal H1N1 influenza is resistant to oseltamivir, said Dr. Anthony J. Fiore.

Call Issued for Greater TB Screening of Immigrants

BY MARY ANN MOON
Elsevier Global Medical News

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 13,293 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," the investigators noted.

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 a 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," Mr. Liu and his colleagues said (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
Elsevier Global Medical News

The Food and Drug Administration said that it had determined that electronic cigarettes marketed by two manufacturers contained 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 at the United States border 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 anabasine, myosmine, and beta-nicotyrine. 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 halt, announced by the NHLBI 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."

THE TRIAL WAS HALTED BECAUSE OF A 38% SERIOUS ADVERSE EVENT RATE IN PATIENTS ON SILDENAFIL, COMPARED WITH AN 8% RATE IN THOSE ON A PLACEBO.

"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. Having 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 began in July 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 treating 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, 26.6% 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 Pa_{O_2} to F_{IO_2} 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 linolenic acid, and antioxidants. The supplements were continued for 21 days or until the patient no longer required mechanical ventilation.

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Acute lung injury patients who took fish oil supplements had fewer ventilator-free days.

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 acid] was deleterious, but it's certainly strongly 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; FluLaval, ID Biomedical Corp.; Fluvirin, Novartis Vaccines & Diagnostics Ltd.; Fluzone, Sanofi Pasteur Inc.; and FluMist, MedImmune Vaccines Inc.

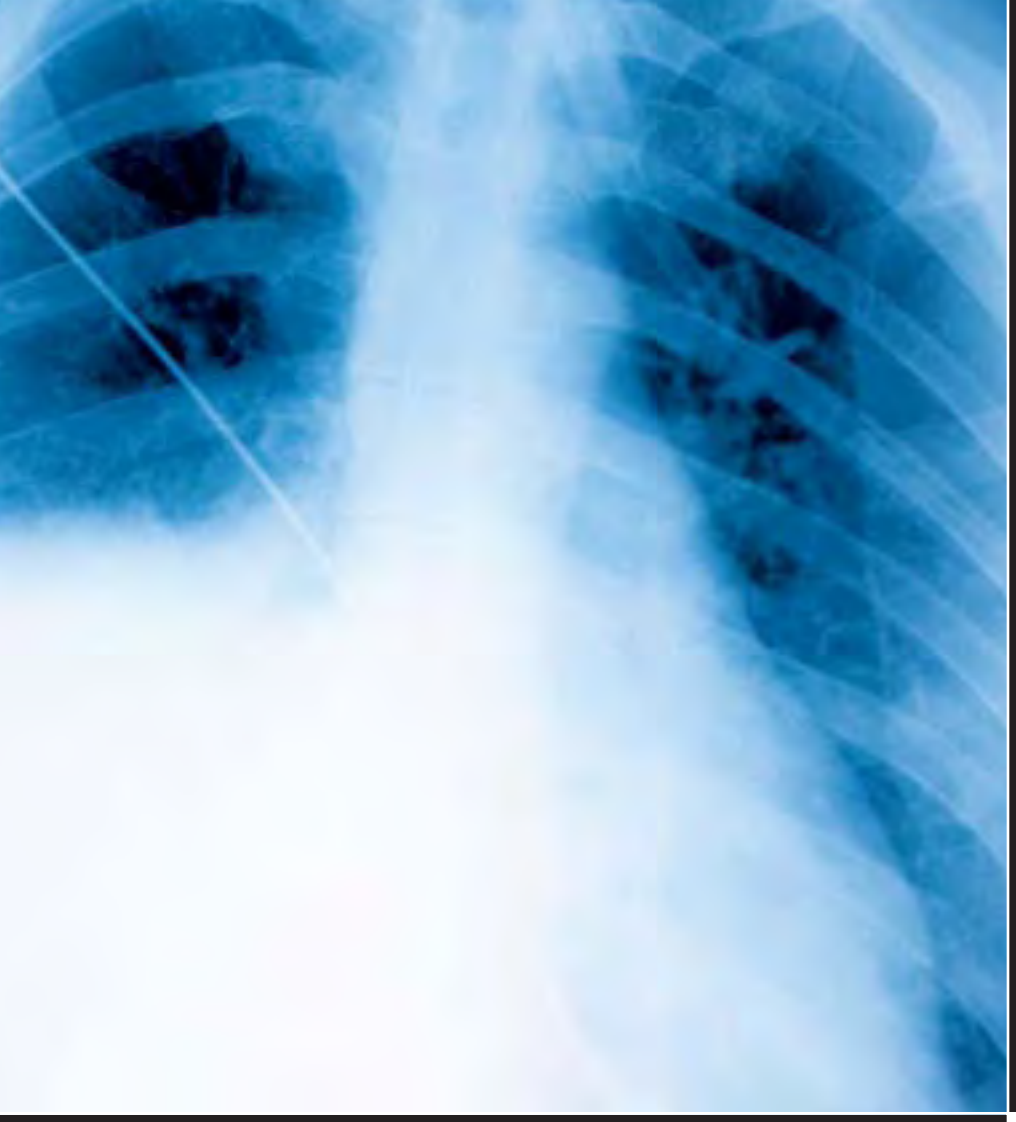
All contain the same three influenza strains, which are predicted to be the predominant circulating strains in the upcoming season: an A/Brisbane/59/2007 (H1N1)–like virus, an A/Brisbane/10/2007 (H3N2)–like virus, and a B/Brisbane/60/2008–like virus.

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 public against the 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:

- ► FDA Web page on Influenza Vaccine Safety & Availability: www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm110288.htm.
- ► FDA List of Strains Included in the 2009-2010 Influenza Vaccine: www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/PostMarketActivities/LotReleases/ucm162050.htm.
- ► Centers for Disease Control and Prevention Web Page on Seasonal Influenza Resources for Health Professionals: www.cdc.gov/flu/professionals/vaccination.
- ► Centers for Disease Control and Prevention Web page with Key Facts About Seasonal Flu Vaccine: www.cdc.gov/flu/protect/keyfacts.htm. ■



SERIOUS INFECTION

SERIOUS RESULTS

ZYVOX—proven efficacy in nosocomial pneumonia, due to known or suspected MRSA[1-3]*

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, vasopressive, and dopaminergic agents.

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid 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-site 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.

Convulsions 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.

IV/Oral

ZYVOX®

(linezolid)

SMART BUG. SMART DRUG.™

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG, and the Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH, for the Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980-992. **3.** Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789-1797.

Please see brief summary of prescribing information on adjacent page.

ZYVOX® linezolid injection, tablets and for oral suspension Brief summary of prescribing information.

INDICATIONS AND USAGE ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (**see PRECAUTIONS, Pediatric Use**). **Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **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. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. **CONTRAINDICATIONS** ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. 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 medicinal 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 types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone. **WARNINGS** **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 have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression.** In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality Imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections**. ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. 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 (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated. **PRECAUTIONS** **General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).** Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. Convulsions 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 use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. *Phenylketonurics:* Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions** ***Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. *Adrenergic Agents:* Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. *Serotonergic Agents:* Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section. **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occured only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. **ADVERSE REACTIONS** **Adult Patients** The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators† (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events‡ were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators§ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events‡ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections‖ with ZYVOX (n=248) or cefadroxil (n= 251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocythemia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections‖ with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1 respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1# respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10^3/mm^3) 0.7 and 0.8; WBC (x 10^3/mm^3) 0.2 and 0.6; neutrophils (x 10^3/mm^3) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10^3/mm^3) 3.0 and 1.8; WBC (x 10^3/mm^3) 2.2 and 1.3 and neutrophils (x 10^3/mm^3) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10^3/mm^3) 0.0 and 0.4; WBC (x 10^3/mm^3) 0.8 and 0.8; neutrophils (x 10^3/mm^3) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10^3/mm^3) 12.9 and 13.4; WBC (x 10^3/mm^3) 12.4 and 10.3 and neutrophils (x 10^3/mm^3) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

* MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‡ The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

§ Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‖ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

¶ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

** <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

†† >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

‡‡ <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

^a^ >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

Rx only

Rev. May 2008

Dartmouth Atlas Examines Hospital, Physician Capacity

BY JOYCE FRIEDEN
Elsevier Global Medical News

A 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. Elliott 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."

AN APPROACH BASED ON ORGANIZED SYSTEMS OF CARE COULD GET BOTH HOSPITAL BED CAPACITY AND THE PHYSICIAN WORKFORCE TO THE RIGHT SIZE.

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 cardiothoracic surgery (–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 overinvested," 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." ■

The report, "Hospital and Physician Capacity Update: A Brief Report from Dartmouth Atlas of Health Care," is available online at www.dartmouthatlas.org/atlases/Capacity_Report_2009.pdf.

Study Puts New Spin on Hypoglycemia-Mortality Link

BY MIRIAM E. TUCKER
Elsevier Global Medical News

Increased mortality associated with hypoglycemia among patients with acute myocardial infarction was not 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 risk 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 insulin therapy 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 episodic hypoglycemia events, which occur in a setting of glucose control with insulin, do not appear to be associated with increased mortality risk. … While continued efforts to avoid hypoglycemia are 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).

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 random blood 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

events was similar between the group of patients who developed hypoglycemia spontaneously and those who became hypoglycemic following insulin initiation.

Overall in-hospital mortality was significantly higher among patients with hypoglycemia compared with those without (12.7% vs. 9.6%).

However, the difference in mortality was accounted for solely by the subgroup of patients who were not treated with insulin (18.4% vs. 9.2%).

In contrast, among those who did receive insulin, mortality was nearly identical between those who did and did not develop hypoglycemia (10.4% vs. 10.2%).

The investigators found that the same trend in mortality persisted after adjustment for a long list of potential confounders, including demographic factors such as age, sex, and race; comorbidities including diabetes, heart failure, and hypertension; in-hospital procedures including revascularization; and medications taken in the hospital, including aspirin, clopidogrel, beta-blockers, statins, and oral antihyperglycemic agents.

After a full multivariate analysis was performed, hypoglycemia was found to 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 who were treated with insulin, there was no significant relationship between hypoglycemia and mortality (OR 0.92).

The investigators also found that excluding patients 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 pointed out that while intensive glucose management has been actively promoted in intensive care units for patients with either known diabetes or "stress" hyperglycemia, enthusiasm for the practice has been tempered recently, as several observational studies have suggested that it is associated with hypoglycemia and worse outcomes (JAMA 2009;301:1599-01).

While the current study "seeks to provide some reassurance that the major risk associated with hypoglycemia is

The study does not directly refute previous concerns that intensive glucose control may be linked to worse outcomes.

DR. NATHAN

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 Dr. Kosiborod by the Cerner Corporation. The funders had no role in the study, however, the report said. Dr. Kosiborod disclosed that he has served on the advisory board of Sanofi-Aventis and has received speaking honoraria from the Vascular Biology Working Group and DiaVed Inc. 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 topics. It also includes audio spots on diabetes, osteoarthritis, preventive health, and more. Visit the Web site at www.ahrq.gov/consumer/espanoix.htm. ■

Vaccine Refusal Radically Increased Pertussis Risk

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

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 were 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.

Dr. Bergen, chair of the pediatric infectious disease section at Kaiser Permanente of 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.

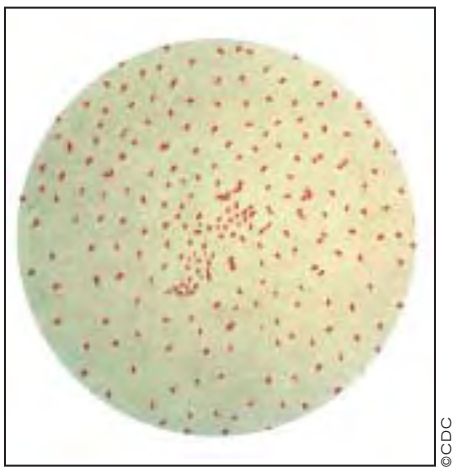
The study examined pertussis vaccination rates and disease prevalence in children aged 2 months to 18 years enrolled in the Kaiser Permanente of Colorado health plan between 1996 and 2007. Each case of pertussis was matched to four randomly selected controls.

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 five 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.



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Vaccine refusers were 23 times more likely to contract *Bordetella pertussis*.

"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 confident 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 as a parent, 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. Flory 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 a data warehouse that links administrative data to clinical and 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 infection. 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 via heliox showed 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
Elsevier Global Medical 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 patients, 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 they gave included that no one had told them that a flu shot was needed for their child (15%); 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. ■

FYI

Inhalant Abuse Info for Teens

The Substance Abuse and Mental Health Services Administration is offering a new publication on inhalant abuse specifically aimed at teenagers. "Tips for Teens: The Truth About Inhalants" provides facts on the long- and short-term effects, the physical and psychological risks, and the legal implications of inhalant abuse. To download the document, go to http://ncadi.samhsa.gov/govpubs/phd631.

Pain Reliever Misuse

The proportion of adults aged 18-25 years who currently use pain relievers for nonmedical reasons rose from 4.1% in 2002 to 4.6% in 2007, but such use declined among teens aged 12-17 years, from 3.2% to 2.7%, according to a report from the Substance Abuse and Mental Health Services Administration. The full report is available online for download at http://oas.samhsa.gov/2k9/painRelievers/nonmedicalTrends.cfm.

BY DR. JAMES A. L. MATHERS, JR., FCCP

PRESIDENT'S REPORT
Advocacy and The CHEST Foundation

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 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(Hon). 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 compassionate, 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 Advances 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 humanistic 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 honoring 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.

THE ATTITUDE OF THE LEGISLATORS REMINDED ME OF THE OFTEN TOO FREQUENT PUBLIC PERCEPTION OF PHYSICIANS AS MENDACIOUS AND SELF-SERVING.

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 donated 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 and other 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
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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 *Annals* article, the editorial, and other information are available at www.chestnet.org/vaccinations/index.php. ■

The CHEST Foundation Awards Two Grants in VTE

With the support of sanofi-aventis, US, The CHEST Foundation announced a request for proposals 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-based replicable 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 their proposal.

A panel of four ACCP members, chaired by Dr. Pascal O. Udekwu, FCCP, convened via conference calls to develop the application, review 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 completing 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 received, from 12 states and 3 countries. Using a detailed grading rubric, the committee selected two ACCP members to receive the grants. The first grant recipient is Dr. Eli A. Akl, MPH, of the Research Foundation of SUNY, University of Buffalo, Amherst, NY. His project is "Developing and Pilot Testing a Novel Outcome Performance Measure for the ACCP Recommendations for the Prophylaxis and Management of Venous Thromboembolism." The first goal in Dr. Akl's proposal is in clinical care: to involve oncologic patients with VTE in shared decision making on the type of long-term anticoagulation used. His outcome objective is to increase the percentage of oncologic patients with VTE sharing in the decision making 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 increase the percentage of oncologic patients with VTE who use this tool to measure performance.

The second grant recipient is Dr. Timothy 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 tool kit for 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 kit on the ACCP Web site to be downloaded by members to reduce or eliminate hospital-acquired VTE within their health-care systems. Dr. Morris' second goal relates to buy in: to provide a process by which clinicians in each health-care system can individualize VTE prevention protocols through their own evidence-based review and expertise. His second outcome objective is to create a CME-based procedure for participating members to review primary literature relevant to the VTE protocols they plan to adopt. The third goal is to establish permanence and promote 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 hospital-acquired VTE, before and during the institution of a formal program.

Both award recipients will carry out their projects over the next year and are required to submit quarterly written reports to The CHEST Foundation. A Webinar will be produced after April 2010, incorporating the educational benefits of each of the projects.

The CHEST Foundation extends congratulations to Dr. Akl and Dr. Morris and appreciation to sanofi-aventis, US, for its support of this important initiative. ■

Pulmonary Perspectives

Déjà vu All Over Again: The Ongoing LABA Controversy

There have been safety concerns about inhaled long-acting beta2-agonists (LABA) for at least 16 years. Since1993, when the results of the Serevent Nationwide Surveillance (SNS) study were reported (Castle et al. *BMJ* 1993; 306:1034). This was a study of 25,180 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, *ie*, 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 Multicenter Asthma Research Trial—or SMART) began in 1996, with the specific intent of determining whether salmeterol use in asthma was associated with an increase in respiratory (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 [GSK]; 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]; Kenilworth, NJ, approved for use in 2001).

The FDA posed four questions to this 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 about the role that inhaled corticosteroids (ICS) might play in mitigating LABA-associated risks. The committee suggested various approaches to revising LABA labels in ways to address the pediatric issues and to express uncertainty about whether concomitant ICS use reduces LABA 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 pharmaceutical and FDA presentations 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 treatment.

At about the same time as this advisory committee meeting, Bateman and colleagues published a metaanalysis of data from 66 GSK trials involving 20,966 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 2006), 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 effect of LABA use on this outcome. 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 concentrated 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 revision to 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; 360:1592). The cynical observer might actually say that not much has changed since the SNS trial 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 databases, 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? How 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 (NAEPP EPR 3, 2007, NHLBI), 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. ■

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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. The meeting followed up a March 2008 roundtable on *Low-Molecular-Weight Heparins: Patient Safety and Clinical Data Requirements for Follow-on "Generic" Biologic Compounds*.

LMWH Regulatory Issues

Should the FDA, acting under the authority of the Drug Price Competition and Patent Term Restoration Act of 1984 (also called the Hatch-Waxman Act) approve LMWH follow-on "generic" versions of branded drugs by an abbreviated process?

The Act allows the FDA to approve abbreviated new drug applications for generic versions of approved reference-branded drugs, relying on prior determination of efficacy and safety of the reference products. The need for clinical trials of the generic version of the branded drug is eliminated. The manufacturers of a generic drug must provide the FDA with complete information about the generic product to ensure that the generic is pharmacologically 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

The physicochemical characterization of unfractionated heparin (UFH) and LMWH is incomplete. The functions of portions of the molecules are not completely understood; these molecular segments may contribute to the immunogenetic 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.

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

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 animals 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 Cosmetics 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

Continued on following page

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rely for approval on certain existing scientific knowledge about the safety and efficacy of the approved protein product." Unlike LMWH, human growth hormone is well characterized and its mechanism of action well understood.

The approval of Omnitrope is not evidence of the establishment of a new process for approval of all follow-on protein products. There has not been a regulatory process for approval of follow-on products of biologic origin, in part because of lack of appropriate statutory support for such a process.

The European Medicines Agency has adopted the term "biosimilar" for the type of drugs the FDA identifies as "follow-on." No biosimilar drug has yet been approved in Europe.

A regulatory pathway for follow-on drugs of biologic origin, whether the origin is natural or biotechnologic, is under development in Congress. The current issues in this debate cover a broad range of patient safety and intellectual property matters.

Of particular interest, the LMWHs may not be directly addressed by this legislation because they have been previously approved as drugs rather than biologics. LMWHs are not unique, as there are approximately 40 other products in this regulatory "no man's land."

Should Clinical Trials Be Required for Approval of Follow-on LMWH Drugs?

In the clinical setting, physicians expect generic drugs to be faithful duplicates of their reference-branded drugs. The physician wants to be assured of a generic's reproducibility of pharmacologic activity and adverse effect profile in the same patient populations that receive the branded drug.

Given that branded LMWHs are uniquely different from one another by reason of biologic starting material and proprietary manufacturing processes, and that each branded LMWH drug has been regarded by the FDA as a unique product requiring clinical trials for approval of each indication, should follow-on LMWHs (1) be approved by the same approval process as that for chemical generics, in which clinical trials are not required; or (2) be required to undergo clinical trials as if they were new drugs? If the latter is deemed most appropriate, what should be the criteria for clinical trials with regard to the study design, patient population(s), efficacy and safety end-points, and trial duration?

Why Clinical Trials Are Not Needed

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

► *Cost.* The expense of company-funded clinical trials in various patient populations for extended periods of time will add significantly to the cost eventually charged for the follow-on drug. This negates the primary reason for making generic drugs—to lower the drug cost.

► *Assumed Efficacy and Safety.* On the basis of data furnished to the FDA by a manufacturer, and by postmarketing surveillance of the branded-reference 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/IIa 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 physiologic functions of the majority of its 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. Like 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 reveals 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, a substantial number 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/IIa activity satisfactorily close to that of the branded product and provided that it satisfactorily meets standards for other assays required by the FDA. ■

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This roundtable was supported by sanofi-aventis. *The proceedings of the March 2008 roundtable along with the list of references may be viewed online by visiting www.chestnet.org/downloads/about/chestPhysician/Sept08supplement.pdf.*

Product of the Month

WEBCAST – Early Detection of COPD: A Clinical Controversy

The use of spirometry for the early detection of chronic obstructive pulmonary disorder has become a topic of controversy since 1999. That was the year that *CHEST* published the National Lung Health Education Program guidelines recommending office spirometry testing for all smokers over the age of 45 years.

The benefits of drug therapy when the FEV_1 is above 50% predicted are disputed, while only one in four patients with a new diagnosis of COPD has undergone spirometry testing to confirm airway obstruction.

In this webcast, two members of NLHEP discuss the evidence both for and against having large national programs that provide screening or promote case-finding for COPD.

Critical Care Commentary

Monitoring Technology in the ICU: An Iconoclastic View

Devices incorporating monitoring technology and intensive care medicine are wed to one another. To many physicians, intensive care equals more monitoring. At their core, intensivists love these devices, the newer the better, and intensivists are especially data-driven, which, in a vicious cycle, drives their desire to use more devices.

However, almost all evidence reveals that more monitoring does not improve outcome; in fact, more monitoring may worsen outcome, or at the very least, increase cost and complexity while yielding no benefit. Yet, a significant portion of the critical care community in practice and in print prefers to ignore these findings that are part and parcel of our history dating back 50 years.

The oldest example of the schism between evidence and practice is measurement of central venous pressure (CVP). It is a completely false, but widely held, belief that the CVP can be used to estimate intravascular volume status. Furthermore, even physicians cognizant that CVP has no relationship to intravascular volume often adhere to an equally false belief that the trend of the CVP over time correlates to the trend in intravascular volume. These beliefs are physiologically illogical (Gelman. *Anesthesiology* 2008; 108:735) and are clinically bereft as a recent systematic analysis of the 24 relevant studies clearly demonstrates (Marik et al. *Chest* 2008; 134:172).

Amazingly, however, the CVP remains one of the most commonly measured variables in the ICU and is even featured as a main decision point in the Surviving Sepsis Campaign algorithm!

The progeny of the CVP monitor is the pulmonary artery catheter (PAC) that expanded hemodynamic data from CVP to include cardiac output (CO), pressures in the pulmonary artery, and mixed venous samples. The PAC seemed to represent a great physiologic advance and was widely accepted within only a few years of its clinical introduction without rigorous evaluation of its benefit in critically ill patients. Problems with the PAC were originally thought to be technical in nature and related to the potential failure of the measured wedge pressure to accurately estimate the left atrial pressure. Later, widespread errors in PAC use, most importantly, user errors in obtaining and interpreting the wedge pressure, were demonstrated. More troubling, over the past decade, several high-quality retrospective studies and prospective randomized trials (*eg*, ESCAPE, ARDSnet, PAC-Man) have all failed to demonstrate an improvement in patient outcome associated with PAC use. Several of these investigations 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, and less invasively, is now 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 systems reliant upon bioreactance (*eg*, NICOM Reliant [Cheetah Medical; Portland, OR]), bioimpedence (*eg*, BioZ [CardioDynamics Inc; San Diego, CA]); TEBCO [Hemo Sapiens Inc; Irvine, CA]), and carbon dioxide rebreathing (NICO [Philips Respironics; Murrysville, PA]), and I will, therefore, focus on them.

As a group, arterial waveform-based devices are frequently lumped together as "noninvasive CO monitors," but they significantly differ from one another, and each yields hemodynamic data other than CO. Their noninvasive CO monitoring technology incorporates measurement of the effect of positive pressure ventilation on the arterial pulse pressure (arterial pulse pressure variation) that supposedly predicts fluid responsiveness. Sophisticated algorithmic analyses of the arterial pressure waveforms yield continuous CO amongst other variables. Arterial pulse pressure may help predict fluid responsiveness better than any other measurement available, but its use has not been subject to a large prospective, randomized, controlled study. Nonetheless, these devices have already been widely used in Europe and are just gaining a foothold in the North American market.

Cardiac output is either determined through a mathematically advanced algorithm that requires no calibration (Flotrac/Vigileo and LiDCO [the *rapid* model]) or the CO must be calibrated to another method (PiCCO and the original LiDCO [the *plus* model]). The mathematics behind the determination of CO without calibration is proprietary and is unintelligible to almost anyone without an electrical engineering degree. Additionally, the algorithms, unfortunately, have also undergone multiple iterations, suggesting that the earlier versions, and perhaps the current versions too, are really not that accurate. The CO and stroke volume variation (SVV) obtained from any one of these noninvasive devices may vary significantly from that simultaneously obtained by another one of these same devices. Also, the SVV determination can only be determined in the presence of positive pressure ventilation and sinus rhythm.

The CO measurements, however, have never been shown to improve outcome. It is possible that the failure of the PAC may be secondary to the fact that CO measurement cannot actually be used in a clinically advantageous fashion. Also, all new devices have their CO "verified" in development to the PAC's CO, using Bland Altman analysis and the principles of Critchley and Critchley (Critchley LAH, Critchley JA. *J Clin Monit Comput* 1999; 15:85). Thus, there is an industry-wide standard allowing the CO reported by one of these devices to vary by as much as 30% from the actual CO.

Noninvasive CO technology may, in fact, be burdensome and complicated. For example, the PiCCO device has specific catheter requirements that usually mandate femoral or axillary artery insertion of a proprietary arterial catheter with a temperature sensor at the tip and placement of a central venous catheter with its tip in the superior vena cava. 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 upon 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 warrant 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 positive fluid balance and a longer duration of mechanical ventilation. Given that PACs may worsen outcome, or at least do not improve outcome, an investigation comparing a new device to the PAC is not what the critical care community should use to base a potential major change in clinical practice.

The original LiDCO device (LiDCO LtD, UK), much like the PiCCO device, requires the CO to be measured in order to "calibrate" its internal algorithm. It utilizes a peripheral injection of lithium ion 0.15 to 0.3 mMol with a 15-mL saline solution flush and a proprietary arterial catheter containing a lithium sensor to construct a dilution curve for the lithium ion. Lithium injections may be problematic, as hyponatremia, lithium carbonate, and other drugs that contain quaternary ammonium ions (*eg*, some muscle relaxants) may interfere with a lithium injection as a calibrating standard.

A randomized trial comparing the LiDCO device coupled with a goal-directed strategy vs conventional management showed a reduction in complications and hospital length of stay after major surgery in the treatment group but no difference in mortality (Pearse et al. *Crit Care* 2005; 9:R687). This was a small study (122 patients), and the groups were not comparable, as the treatment group received dopexamine, a medication not given to patients in the control group and not available in North America.

Although the FloTrac/Vigileo system is used with a standard arterial catheter, it 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 (Biancofiore et al. *Br J Anesthesiol* 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 change. However, we must guard against the errors we made in the past as exemplified by CVP and PAC monitoring. Prospective investigation emphasizing the impact the noninvasive CO devices have on 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

Dr. Neil Halpern, FCCP

Editor,
Critical Care Commentary

Pulmonary Medicare CAC Update

BY DR. ANTHONY MARINELLI, FCCP, ACCP CAC CHAIR; DIANE KRIER-MORROW, MBA, MPH, CCS-P, ACCP CONSULTANT; AND MARLA BRICHTA, ASSISTANT VICE PRESIDENT, ACCP PRACTICE MANAGEMENT DEPARTMENT

The ACCP Practice Management Department invites your participation on the ACCP Contractor Advisory Committee (CAC). In addition to the important work of Dr. Steve Peters, FCCP, as the ACCP CPT Advisor, and Dr. Scott Manaker, FCCP, as the ACCP RVS Update Committee (RUC) Advisor, and his alternate, Dr. Burt Lesnick, FCCP, and their ATS colleagues, 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 administrators 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 decisions (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 contractors 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 representatives to discuss the CAC process and issues of interest.

During a recent conference call of the multisociety Critical Care Workgroup (CCWG), Dr. Andrew Bloschiak, MBA, Jurisdiction #12 CMD for Highmark Medicare Services, the Medicare Administrative Contractor (MAC) for Delaware, Maryland, New Jersey, Pennsylvania, and Washington, spoke to the group about edits identified by ACCP CAC that were inappropriately denying payment of claims for appropriately reported and documented 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 individually, 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 payments submitted beyond 120 days of the 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 expeditious way Highmark 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 alternate representative for each state who can assist in this important work of representing 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 section of *CHEST*. They noted the inappropriate use of CPT 94725 membrane diffusing capacity by independent diagnostic testing facilities (IDTF). The ACCP and ATS brought the issue to the attention of Medicare, and some CAC members brought the issue to the attention of their MAC or contractor medical directors. The reference in *CHEST* and the link to this article is: The Carbon Monoxide Diffusing Capacity: Clinical Implications, Coding, and Documentation. *Chest* 2008; 134: 663-667; 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 identify CAC representatives in these states: Colorado, Idaho, Missouri, North Carolina, 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. ■

NetWorks
Tobacco Regulation, On-Screen Use of Tobacco

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 effects of nicotine on lung cancer therapy, particularly with the smallest concentration, such as that in nicotine supplements, the new role of the FDA encompasses the opportunity to demand changes in tobacco products that may have significant impact on the morbidity, response to cancer therapy, and mortality in patients with cancer.

The overwhelming majority of lung cancers are associated with smoking and are caused by carcinogen-induced gene mutations and subsequent tumor development. However, tumor promoters, such as nicotine, appear to be contributing factors to the progression, growth, metastasis, and inhibition of response to treatment of lung cancers (Zhang et al. *Am J Respir Cell Mol Biol* 2009; 40:135; Zheng et al. *Am J Respir Cell Mol Biol* 2007; 37:681). Continued smoking was noted to be associated with disease progression and resistance to cancer therapy and was the strongest negative factor affecting survival in patients with lung cancer (Videtic et al. *J Clin Oncol* 003;15,1544).

The new role of 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 Marinelli, FCCP,
Chair, ACCP CAC;
and Diane Krier-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 Women'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 Amaalliance.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

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 Ultrasonography-Guided Transbronchial Needle Aspiration in Patients With Suspected Sarcoidosis.** *By Dr. A. Tremblay, et al.*

▶ **Contamination of Portable Radiograph Equipment With Resistant Bacteria in the ICU.** *By Dr. P. D. Levin, et al.*

▶ **A Postmortem Analysis of Major Causes of Early Death in Patients Hospitalized With COPD Exacerbation.** *By Dr. B. Zvezdin, 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. G. Raghu, on behalf of the IPFnet.*

SPECIAL FEATURE

▶ **A History of Tuberculosis on Stamps.** *By Dr. M. A. Shampo, and Dr. E. C. Rosenow III, Master FCCP.*

COMMENTARY

▶ **Safety of Long-Acting Beta-Agonists: Are New Data Really Required?** *By Dr. M. R. Sears.*

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 education 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 30 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 free lunch. Look for specially marked "Have Lunch With the Experts" areas or lunchtime 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.

CHEST 2009
October 31 - November 5
San Diego, California

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. ■

Ambassadors Program Is Back for CHEST 2009

"Celebrating Our Diversity," is an exciting new program that debuted at CHEST 2008, sponsored by The CHEST Foundation's Ambassadors Group.

THE CHEST FOUNDATION℠
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 Raoof, dressed in beautiful saris, the traditional attire for women living in India. They also displayed the common male attire of the dhoti and kutra.

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. Loraine 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. ■

COURTESY ACCP

From CHEST 2008 Celebrating Our Diversity: L-R, Sabiha Raoof, Anita Mathur, and Pratima Mathur.

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 folk, 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 are authentic chutneys and relishes; 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 brews 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 rather venture farther from 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 PATRICE WENDLING
Elsevier Global Medical News

AUSTIN, TEX. — 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** (Kapidex) 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 30-60 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 nonsteroidal that we are also providing."

► **Sancuso** is 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 Haldol (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.

► **Metoclopramide** drugs, which include Reglan (metoclopramide) tablets and injections, received a black box warning in February because chronic use has been linked to tardive dyskinesia. Patients at the end of life typically are treated with up to 40 mg a day of metoclopramide for less than 3 months, but caution should be used in elderly patients, especially women, and in those receiving both Reglan and Haldol, said Dr. McPherson.

► **Tapentadol**, a centrally acting analgesic with potency between those of morphine and tramadol, was approved at the end of 2008 for relief of moderate to severe acute pain in adults. Although tapentadol is not approved for chronic pain, it may be of use in hospice and palliative care, Dr. McPherson said. Tapentadol 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. ■

Morning Headache Common in Sleep Disorders

BY DOUG BRUNK
Elsevier Global Medical News

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.

CPAP therapy appeared to improve headache symptoms among patients who were CPAP compliant.

DR. QUAST

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/m^2, and 66% were male.

A total of 154 patients (70%) 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. ■

To view a video interview of Dr. Quast, visit www.youtube.com/watch?v=NwQtK9rtvNI.

Sleep Apnea May Independently Point to Type 2 Diabetes

BY SUSAN LONDON
Elsevier Global Medical News

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.

Participants with moderate or severe OSA had a significant near doubling of the risk of diabetes.

DR. TOGEIRO

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 37 years vs. 48 years and 53 years, respectively), had a higher body mass index (25 kg/m^2 vs. 28 and 30 kg/m^2), 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 mild 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 risk (odds ratio 1.97).

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

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