



# CHEST *Physician*

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



COURTESY ACCP

Dr. Kalpalatha Guntupalli presents the Presidential Medal to Dr. David D. Gutterman. See pp. 18-21 for more from CHEST 2010.

## Healthy People 2020: Sleep Health New Goal

BY SHARON  
WORCESTER

*Elsevier Global Medical News*

The Department of Health and Human Services has launched its Healthy People 2020 goals, and among the objectives set forth in its “ambitious, yet achievable” 10-year agenda for improving the nation’s health are substantial improvements in sleep health, respiratory disease outcomes, and levels of tobacco use.

### Sleep Health

Sleep health is a new topic in the Healthy People initiative. The main focus is on increasing public knowledge of how adequate sleep and treatment of sleep disorders improves health, productivity, wellness, quality of life, and safety on the roads and in the workplace.

“Poor sleep health is a common problem, with 25% of U.S. adults reporting insufficient

sleep or rest at least 5 out of every 30 days,” the report states.

The public health burden is substantial, and awareness of the problem is lacking; thus, Healthy People 2020 seeks to provide a “well-coordinated strategy to improve sleep-related health.”

Objectives are to:

- ▶ Increase the proportion of persons with symptoms of obstructive sleep apnea who seek medical care (from 25.5% to 28%).
- ▶ Reduce the rate of vehicular crashes per 100 million miles traveled that are due to drowsy driving (from 2.7 to 2.1).
- ▶ Increase the proportion of students in grades 9-12 who get sufficient sleep, defined as 8 hours or more on an average school night (from 30.9% to 33.2%).
- ▶ Increase the proportion of adults who get sufficient sleep, defined as 8 or more hours for

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## Lung Reduction in Emphysema Aids Select Patients

*‘The survival after LVRS is excellent.’*

BY SUSAN LONDON  
*Elsevier Global Medical News*

VANCOUVER, B.C. – Lung volume reduction surgery is safe and effective for the treatment of advanced emphysema in appropriately selected patients, according to the experience at Columbia University Medical Center, New York.

Among 49 patients who underwent LVRS at the center during a period of roughly 5 years, all of whom fell into group 1 or 2 as previously established by the National Emphysema Treatment Trial (NETT), none died within 90 days. Some 43% experienced air leaks, but the leaks were manageable.

The patients had a 3-year actuarial survival rate of 95%, and their BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, used to estimate prognosis in this population, fell from 4.9

preoperatively to 2.6 at 1 year on a scale ranging from 0 to 10.

“Surgical LVRS should be considered the treatment of choice for patients with upper lobe–predominant emphysema meeting selection criteria established by NETT,” Dr. Mark Ellis Ginsburg said in a presentation of study results at CHEST 2010, the annual meeting of the American College of Chest Physicians. “I think it is the gold standard against which new technologies should be judged.”

However, just 119 LVRS procedures were performed in the United States in 2008, despite the favorable NETT findings for certain patients and coverage of the procedure by the Centers for Medicare and Medicaid Services for qualifying patients and centers.

He speculated that pulmonologists’ poor view of LVRS

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## H1N1 Influenza Still a Threat to Kids

BY LAIRD HARRISON  
*Elsevier Global Medical News*

LAS VEGAS – It’s not over yet. Though the H1N1 2009 pandemic influenza strain did not wreak the havoc that was feared, it killed more children than its seasonal flu cousins last season and may well repeat that performance if not enough people get vaccinated,

according to Dr. Christopher J. Harrison of Children’s Mercy Hospital in Kansas City.

“Maybe it didn’t kill as many adults, but children were disproportionately affected,” said Dr. Harrison, who is also director of the Infectious Disease Research Laboratory and professor of pediatrics at the University of Missouri–Kansas City School of Medicine, in a

presentation at a pediatric update sponsored by the American Academy of Pediatrics California District 9. “Pregnant women were disproportionately hit as well.”

This season, public health authorities are recommending vaccination for everyone who is 6 months of age or older. If at

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**#1**



## DYNAMIC DUO

Thanks for making **CHEST** and **CHEST Physician** the top 2 publications read by pulmonologists!

(Kantar Media Medical/Surgical Readership Study, December 2010)

**#2**



**November was Pulmonary Hypertension Awareness Month.  
Here's how you can help.**

# Don't wait, **refer early**

- Early referrals to a PH Specialist help provide comprehensive care<sup>1-3</sup>

**Turn the page to learn about the advantages  
of early referrals to PH Specialists...<sup>1,2</sup>**



**November was Pulmonary Hypertension Awareness Month.  
Here's how you can help.**

# Don't wait, refer early

**PH Specialists encourage early referrals of PAH patients  
regardless of WHO Functional Class (I, II, III, IV)\*<sup>1-4</sup>**

**Patients receive comprehensive care**

- A full support system for PAH patients, including comprehensive medical care, reimbursement opportunities, education, and counseling<sup>5-7</sup>

**Patients gain access to information on the latest clinical trials<sup>1-3,5-7</sup>**

- Patients' participation helps build clinical trials that provide reliable data relevant to the PAH population<sup>1,3,8,9</sup>

**Help optimize care for your PAH patients with early referrals.**

Please visit [www.PHAssociation.org](http://www.PHAssociation.org) for more information.

**\*Adapted from the New York Heart Association (NYHA).**

**References:** 1. Barst RJ, Gibbs JSR, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;54(1)(suppl S):S78-S84. 2. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol.* 2009;53(17):1573-1619. 3. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest.* 2007;131:1917-1928. 4. McGoon M, Guterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126:14S-34S. 5. Temple University Hospital. Temple Lung Center & Pulmonologists. <http://pulmonary.templehealth.org/content/default/htm>. Accessed September 24, 2010. 6. Stanford University. Stanford Pulmonary Hypertension Program. <http://pulmonary.stanford.edu/patientcare/hyperten.html>. Accessed September 24, 2010. 7. Pulmonary Hypertension Clinic, Mayo Clinic in Rochester, Minn. Cardiovascular Diseases in Minnesota. <http://www.mayoclinic.org/cardiovascular-disease-rst/pulmhyperclinic.html>. Accessed September 24, 2010. 8. McLaughlin VV, Badesch DB, Delcroix M, et al. End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;54(suppl 1):S97-S107. 9. Humbert M, McLaughlin VV. The 4th World Symposium on Pulmonary Hypertension. *J Am Coll Cardiol.* 2009;54:S1-S2.



# New COPD, Tobacco Goals Set

Healthy People • from page 1

those aged 18-21 years, and 7 or more hours for those aged 22 years and older (from 69.6% to 70.9%).

## Respiratory Disease

The respiratory disease category focuses on asthma and chronic obstructive pulmonary disease, and the main goal is to “promote respiratory health through better prevention, detection, treatment, and education efforts,” according to the report, which states that asthma affects 23 million people in the United States and COPD affects 13.6 million U.S. adults.

The cost to the health care system is high, and society pays through higher health insurance rates and lost productivity and tax dollars. Annual expenditures for asthma alone are estimated at nearly \$21 billion.

Healthy People 2020 seeks to reduce asthma-related deaths, hospitalizations, emergency department visits, activity limitations, and missed school or work days, and to increase the proportion of asthma sufferers who receive appropriate care. Improved surveillance at the state level is another goal.

For example, goals for 2020 in regard to asthma-related deaths include reductions from 11.0 to 6.0 deaths per 1 million people aged 35-64 years, and from 43.3 to 22.9 per 1 million people aged 65 and older. Goals regarding annual asthma-related hospitalization include a reduction from 41.4 to 18.1 per 10,000 children under age 5, from 11.1 to 8.6 per 10,000 people aged 5-64 years, and from 25.3 to 20.3 per 10,000 adults aged 65 years and older.

Goals regarding appropriate asthma care include improvements in the number of patients who receive written asthma management plans, instructions for inhaler use, education about appropriate response to an asthma episode, and follow-up visits each year.

COPD-related objectives include reducing activity limitations, deaths, hospitalizations, and emergency department visits, and improving diagnosis among adults with abnormal lung function.

Specific goals include a reduction from 23.2 to 18.7 in the percentage of adults with COPD aged 45 years and older with activity limitations from COPD, and a reduction from 112.4 to 98.5 in the number of COPD-related deaths per 10,000 people aged 45 years and older.

## Tobacco Use

Tobacco use is not a new topic in the Healthy People initiative, but ongoing efforts to reduce use are needed, according to the report, because tobacco use remains the single most preventable cause of death and disease in the United States. About 443,000 Americans die from tobacco-related illnesses each year, and for every 1 who dies, 20 more suffer with at least one serious tobacco-related illness.

Healthy People 2020 seeks to “provide a framework for action to reduce tobacco

use to the point that it is no longer a public health problem for the nation.”

More than 4 decades of evidence has shown that the toll tobacco use takes on families and communities can be significantly reduced by fully funding tobacco control programs, increasing the prices of tobacco products, enacting smoke-free policies, controlling access to products, reducing tobacco advertising and promotion, implementing anti-tobacco media campaigns, and encouraging and assisting users to quit.

Healthy People 2020 addresses tobacco use prevalence, health system changes, and social and environmental changes. Among the key goals for adults are:

- ▶ Reducing the percentage of adult cigarette smokers (from 20.6% to 12.0%).
- ▶ Reducing the percentage of adult users of smokeless tobacco (from 2.3% to 0.3%).
- ▶ Reducing the percentage of adult cigar smokers (from 2.2% to 0.2%).

In adolescents, goals include reducing the percentage of those who used tobacco in the past month from 26% to 21%, and reducing the percentages who said they used cigarettes, smokeless tobacco, and cigars in the past month from 19.5% to 16%, from 8.9% to 6.9%, and from 14% to 8%, respectively.

Initiation of tobacco use among children, adolescents, and young adults is also addressed, with a goal of reducing it among those aged 12-17 years from 7.7% to 5.7%, and among those aged 18-25 years from 10.8% to 8.8%.

Numerous goals are also set in regard to health system changes, and social and environmental changes.

For example, the report calls for increases in comprehensive Medicaid coverage for nicotine dependency treatment, increased tobacco screening and counseling in health care settings, reductions in the proportion of nonsmokers exposed to secondhand smoke, increases in the proportion of persons covered by worksite

policies that prohibit smoking, and increases in tobacco-free environments in school facilities and at school events.

Efforts should be made to eliminate state laws that preempt stronger local tobacco control laws, to reduce illegal sales to minors, and to reduce exposure to tobacco advertising and promotion among 6th-12th graders. Also, federal and state taxes on tobacco products should be increased, the report states.

Healthy People 2020 has been in development since 2007. A panel of health experts drew on input from public and private health officials, preventive medicine experts, representatives from 2,000 health organizations, and thousands of public comments.

The initiative expands upon topics from Healthy People 2010, and will incorporate the Internet and other media in spreading the message. The ultimate goals, according to HHS officials, are to avoid preventable diseases and to promote improved quantity and quality of life. ■



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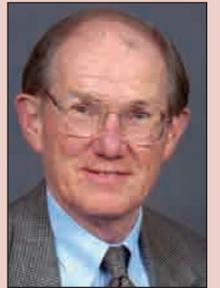
### CHEST PHYSICIAN Is Online

*CHEST PHYSICIAN* is available on the Web at [www.chestnet.org/accp/chest-physician](http://www.chestnet.org/accp/chest-physician).

## COMMENTARY

### Dr. Paul A. Selecky, FCCP, comments:

Each of these topics is very important to good health, and often go hand in hand, e.g., COPD and tobacco use. It's also good news that sleep finally got on the HHS radar. It is the third important pillar of good health, along with regular exercise and a balanced diet. We are a sleep-deprived nation with a “National Sleep Debt,” a term coined by William Dement, a true pioneer in sleep medicine. Sleeping longer on the weekend will not repay that debt.



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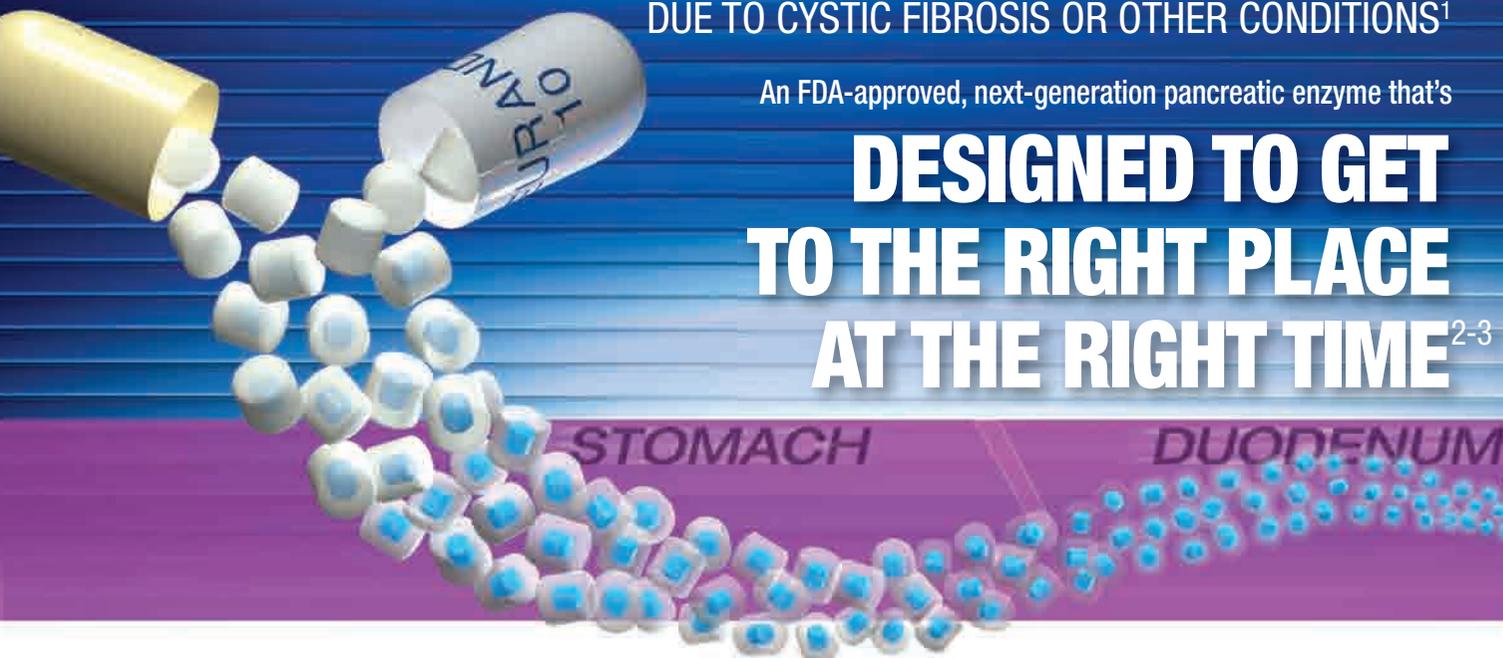


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- 91% (n=29 of 32) of patients achieved a CFA  $>80\%$ <sup>4</sup>
- Results were achieved without the use of concomitant agents such as PPIs, H<sub>2</sub>-antagonists, and motility agents<sup>4</sup>

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- 100% (N=19) of children with PI due to CF switched to ZENPEP from a previous unapproved pancreatic enzyme had improved or maintained their level of symptom control (secondary endpoint)<sup>4</sup>
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  - ZENPEP is not interchangeable with any other pancrelipase product, and requires a new prescription

### Important Safety Information

- Fibrosing colonopathy is a rare serious adverse reaction associated with high-dose use of pancreatic enzyme replacement products and most commonly reported in pediatric patients with CF. Exercise caution when doses of ZENPEP exceed 2500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day)
- Exercise caution when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia and when administering pancrelipase to a patient with a known allergy to proteins of porcine origin
- To avoid irritation of oral mucosa or inactivation of enzymes, do not chew ZENPEP capsules or beads or retain in the mouth
- There is theoretical risk of viral transmission with all pancreatic enzyme products, including ZENPEP

**Please read Brief Summary of Prescribing Information on adjacent page and provide Medication Guide to patients prescribed ZENPEP.**

\*Reports were subjective and recorded in a daily diary form.<sup>4</sup>

**References:** 1. ZENPEP [package insert]. Yardley, PA: Eurand Pharmaceuticals, Inc.; 2010. 2. Data on file MED-0151, Eurand Pharmaceuticals, Inc., Yardley, PA. 3. Data on file MED-0152, Eurand Pharmaceuticals, Inc., Yardley, PA. 4. Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. *J Cyst Fibros.* 2009;8(6):405-417.



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# Cancer Patients Benefit From Earlier Palliative Care

BY SUSAN BIRK

*Elsevier Global Medical News*

CHICAGO – Oncologists and others who care for cancer patients can improve outcomes by integrating palliative care into standard treatment earlier – even as early as the time of diagnosis, Dr. Charles F. von Gunten said at the Chicago Supportive Oncology Conference.

Doing so would require clinicians to expand their definition of palliative care

far beyond the traditional boundaries of hospice, which begins only toward the end of life when other therapies are no longer working, said Dr. von Gunten of the University of California, San Diego, and provost at the Institute for Palliative Medicine at San Diego.

He called on clinicians to rethink the traditional “either-or” approach to cancer treatment – in which care consists of either therapies aimed at reducing or curing the illness or care designed to ease

suffering and improve the quality of life – and to adopt a “both-and” model instead that employs both standard therapies and palliative interventions simultaneously.

Dr. von Gunten noted the growing accumulation of data during the past 20 years demonstrating the effectiveness of palliative care.

One recent study, for example, found that early palliative care significantly improved quality of life and mood among patients with metastatic non-small cell

lung cancer as compared with standard care (*N. Engl. J. Med.* 2010;363:733-42). Although significantly fewer patients in the early palliative care group than in the standard treatment group received aggressive end-of-life care (33% vs. 54%), median survival was significantly longer among patients receiving early palliative care (11.6 months vs. 8.9 months).

“Palliative care delivered by hospice programs in the [United States] is better than standard of care at the end of life,” Dr. von Gunten said. “That has been proven. ... We should get rid of this language of ‘choice’: ‘Hospice is a choice if you want it; antibiotics are a choice if you want it; chemotherapy is a choice if you want it.’ We’re past that. This is the standard of care, and it should be advocated that way by all of us.”

But palliative care still has a way to go before it becomes an integral part of cancer treatment, although some progress has been made, he said. According to a recent survey, 98% of NCI-designated cancer centers and 78% of community cancer centers report having palliative care programs (*JAMA* 2010;303:1054-61).

“This is huge progress from 10 years ago, when they couldn’t even say the word,” Dr. von Gunten said. “However, in most of those places – 92% – it’s just one physician, often part-time.”

More sobering, he said, is a 1998 membership survey by the American Society of Clinical Oncologists in which 90% of oncologists reported “trial and error” as their primary source of information about palliative care. “How enthusiastic would you be about a doctor who was going to take out your anus, and you said, ‘Doctor, how did you learn about this?’ and he said, ‘Oh, trial and error,’” Dr. von Gunten said.

Of those surveyed, 73% said they learned from colleagues and role models. “That’s great, except where did colleagues and role models learn? Trial and error,” he said. And 38% of oncologists said the most significant source of their information about palliative care was a traumatic experience. The underlying message is that no one is teaching palliative care to oncologists, he said.

Dr. von Gunten had no disclosures. ■



Prescription only

**Brief Summary of Prescribing Information** (for Full Prescribing Information and Medication Guide, refer to package insert)

## INDICATIONS AND USAGE

ZENPEP is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions

## DOSAGE AND ADMINISTRATION

### Dosage

ZENPEP is not interchangeable with any other pancrelipase product.

#### Infants (up to 12 months)

- Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.
- Do not mix ZENPEP capsule contents directly into formula or breast milk prior to administration.

#### Children Older than 12 Months and Younger than 4 Years

- Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

#### Children 4 Years and Older and Adults

- Enzyme dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

### Limitations on Dosing

- Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.

### Administration

ZENPEP should be swallowed whole. For infants or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food, e.g., applesauce.

## DOSAGE FORMS AND STRENGTHS

- 5,000 USP units of lipase; 17,000 USP units of protease; 27,000 USP units of amylase. Capsules have a white opaque cap and body, printed with “EURAND 5”
- 10,000 USP units of lipase; 34,000 USP units of protease; 55,000 USP units of amylase. Capsules have a yellow opaque cap and white opaque body, printed with “EURAND 10”
- 15,000 USP units of lipase; 51,000 USP units of protease; 82,000 USP units of amylase. Capsules have a red opaque cap and white opaque body, printed with “EURAND 15”
- 20,000 USP units of lipase; 68,000 USP units of protease; 109,000 USP units of amylase. Capsules have a green opaque cap and white opaque body, printed with “EURAND 20”

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of ZENPEP exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day).
- To avoid irritation of oral mucosa, do not chew ZENPEP or retain in the mouth.
- Exercise caution when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia.
- There is theoretical risk of viral transmission with all pancreatic enzyme products including ZENPEP.
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.

## ADVERSE REACTIONS

- The most common adverse events ( $\geq 6\%$  of patients treated with ZENPEP) are abdominal pain, flatulence, headache, cough, decreased weight, early satiety, and constipation.
- There is no postmarketing experience with this formulation of ZENPEP.

To report SUSPECTED ADVERSE REACTIONS, contact EURAND Pharmaceuticals, Inc. at 1-800-716-6507 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

No drug interactions have been identified. No formal interaction studies have been conducted.

## USE IN SPECIFIC POPULATIONS

### Pediatric Patients

- The safety and effectiveness of ZENPEP were assessed in pediatric patients, ages 1 to 17 years.
- The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase in pediatric patients have been described in the medical literature and through clinical experience.

See **PATIENT COUNSELING INFORMATION** in Prescribing Information and FDA-approved Medication Guide.

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Rev January 2011

## COMMENTARY

**Dr. Paul Selecky, FCCP, comments:** The New England Journal of Medicine study was a hallmark example of the potential impact of palliative care on health quality and quantity of life. Along that line, pulmonologists should provide a treatment program for our patients with progressive chronic lung diseases (COPD, IPF) that includes the specific treatment of dyspnea that persists despite appropriate treatment of the disease. The ACCP Consensus Statement on the management of dyspnea in advanced lung disease can be found in *Chest* 2010;137:674-91.

# Respiratory Events a Risk After Bariatric Surgery

BY DIANA MAHONEY  
Elsevier Global Medical News

LAS VEGAS – Pulmonary complications following bariatric surgery occur infrequently but are associated with significantly increased rates of postoperative morbidity and mortality, according to a large national study that also identified modifiable preoperative risk factors for poor pulmonary outcomes.

In an analysis of data from the American College of Surgeons' 2007 National Surgical Quality Improvement Program (NSQIP) – a prospective database comprising more than 200,000 inpatient and outpatient operations done at 183 representative U.S. hospitals – postoperative pneumonia and postoperative respiratory failure were the most common non-wound-related complications reported among 12,252 patients who underwent bariatric surgery, together accounting for 26% of the overall 30-day morbidity rate, Dr. Prateek K. Gupta said at the annual meeting of the American Society for Metabolic and Bariatric Surgery.

"In comparison, renal complications and cardiac complications accounted for 7% and 2%, respectively, of postoperative morbidity," he noted. The analysis included patients who underwent Roux-Y gastric bypass, adjustable gastric banding, and gastroplasty.

Specifically, postoperative pneumonia was reported in 72 patients and postoperative respiratory failure (defined as reintubation after extubation or a total duration of ventilator-assisted respirations for a period of 48 hours) was reported in 86 patients, said Dr. Gupta of Creighton University in Omaha, Neb.

In patients with postoperative pneumonia, "2.78% died within 30 postoperative days, compared with 0.17% of patients without pneumonia," Dr. Gupta said, and 10.47% of patients with respiratory failure died within 30 days, compared with 0.12% of patients without respiratory failure.

Patients with these pulmonary complications also had significantly longer hospital stays. "The median length of stay for postoperative pneumonia patients was 14 days, compared with 2 days for patients without pneumonia, and a similar, significant trend was observed in patients with respiratory failure," Dr. Gupta reported.

In multivariate analyses, a history of heart failure was a major risk factor for postoperative pneumonia, with an adjusted odds ratio of 10.7. "To our knowledge, [heart failure] was not previously shown to be a risk factor for pneumonia," he noted. "The association could be due to perioperative worsening of cardiopulmonary function,

although the precise reasons are unclear."

Additional risk factors for postoperative pneumonia included history of stroke with neurologic deficit (OR, 9.8), consumption of more than two alcohol drinks per day (OR, 9.0), history of severe COPD (OR, 4.5), an open wound (OR, 3.8), and higher American Society of Anesthesiologists Physical Status classification (OR, 2.0), Dr. Gupta said.

With respect to postoperative respiratory failure, "patients with a history of myocardial infarction within 6 months prior to surgery had 50 times increased risk for this complication," he said.

Other preoperative risk factors for respiratory failure included receiving a preoperative transfusion of more than four units of blood within 72 hours of surgery (OR, 19.0), consumption of more than two alcohol drinks per day (OR, 7.8), history of severe COPD (OR, 4.6), and hypertension (OR, 2.4), Dr. Gupta reported.

Patients whose bariatric surgery was deemed "emergent" were six times more likely to experience respiratory failure than were those who had nonemergent procedures, "but the nature of the emergencies was unclear," Dr. Gupta noted.

Awareness of the preoperative risks that might lead to pulmonary complications is important for patient optimization and selection prior to surgery, Dr. Gupta stressed.

The use of specific strategies to optimize modifiable risk factors in bariatric patients may help "control the incidence of postoperative pneumonia and respiratory failure, thereby improving surgical outcomes," said Dr. Gupta, who reported having no relevant disclosures. ■

COMMENTARY

**Dr. Jeana O'Brien, FCCP, comments:** This report by Dr.

Gupta provides interesting, but not surprising, information about an increased frequency



of pulmonary complications in bariatric surgery patients. Unfortunately, the NSQIP database does not include all the elements necessary to further ascertain all important risk factors. This information should alert bariatric specialists to the need for frequent inclusion of pulmonologists in the preop as well as postoperative care of these patients on a routine basis.

## Patients Met NETT Criteria

Emphysema • from page 1

is the main factor contributing to its underuse. "Most pulmonologists do not support this procedure," commented Dr. Ginsburg, who is associate director of the division of general and thoracic surgery at Columbia University in New York. "We have some pulmonologists who have had great experiences and continue to send us patients, but I think the vast number of pulmonologists do not send patients."

His center has had a multidisciplinary LVRS team for 15 years, he noted. Between January 2004 and April 2009, the team performed the surgery on patients with emphysema who strictly met the NETT inclusion and exclusion criteria, as well as all CMS selection requirements.

Only patients falling into NETT group 1 (upper lobe-predominant disease, low exercise capacity) or group 2 (upper lobe-predominant disease, high exercise capacity) were included, he said. Patients with non-upper lobe-predominant disease (group 3 or group 4) or high-risk features were excluded.

On average, the 49 patients

were 63 years old and had an FEV<sub>1</sub> (forced expiratory volume in 1 second) of 25% of predicted, a carbon monoxide diffusing capacity of 27% of predicted, and a maximal workload of 37 watts. They were nearly equally split between group 1 and group 2.



**LVRS 'can be performed with very low surgical risk, significant benefit, and fairly predictable results.'**

DR. GINSBURG

All of the patients underwent bilateral LVRS. Twenty percent had their surgery through a median sternotomy, before 2005, when the center switched to video-assisted thoracic surgery.

"We try to take out anywhere from 30% to 40% of the lung volume to really make room for the remaining good lung to ventilate. ... We have to be fairly aggressive with this operation," he noted. "The goal of lung reduction is really to allow the good lung space to inhale and overcome the inspiratory restraint that exists in these patients."

None of the patients died during surgery, their hospital stay, or the first 90 postoperative days, Dr. Ginsburg reported.

They had a median length of stay of 8 days. Most (92%) were discharged to home, while the rest were discharged to an inpatient rehabilitation facility.

"Of note, 47% of our patients had no major complications," he commented. By far, the leading major complication was a prolonged air leak (one lasting more than a week), seen in 43%. But these leaks were manageable mainly with Heimlich valves that were removed at follow-up office visits.

"The air leak issue, even though it [is common] and certainly leads to prolonged length of stay in these patients, I think clinically it's not that big of an issue," Dr. Ginsburg said.

Among other complications, two patients had to be reintubated and receive a tracheostomy, but both were weaned off the ventilator and extubated before discharge. Three patients developed pneumonia.

"The survival after LVRS is excellent," with 1- and 3-year actuarial rates of 98% and 95%, respectively. "If you think about what you'd expect in actual survival for patients who have a preoperative FEV<sub>1</sub> of 25%, I think in and of themselves these are fairly impressive numbers."

Among the 44 patients with follow-up data, the BODE index fell from 4.9 preoperatively to 2.6 at 1 year (*P* less than .0001).

"One of the criticisms of early data for lung reduction was that there was a significant amount of missing data, and missing data skewed the results to benefit surgery," Dr. Ginsburg commented.

Therefore, the analysis was repeated with imputation of the worst possible scores for the five patients with missing data. The BODE index still fell significantly, from 4.9 to 3.0 (*P* less than .0001).

On average, the reduction in this index was greater among

group 1 patients than among their group 2 counterparts (–2.9 vs. –1.9; *P* less than .02).

Patients also had significant improvements in all four of the individual components of the BODE index before imputation, and in two of the components (FEV<sub>1</sub> and dyspnea index) after imputation of worst possible values for the patients with missing data.

"LVRS now, in 2010, using the lessons from NETT, can be performed with very low surgical risk, significant benefit, and fairly predictable results," Dr. Ginsburg concluded.

Dr. Ginsburg reported that he is a consultant for PneumRx. ■

COMMENTARY

**Dr. Richard Fischel, FCCP, comments:** This article discusses a very interesting point. Despite a nationwide and very expensive study sponsored by the NIH known as the NETT or national emphysema treatment trial which showed a significant improvement in quality of life for patients undergoing LVRS or lung volume reduction surgery, the procedure is infrequently performed. The results discussed from the Columbia University experience are excellent and consistent with those achieved at quality programs with appropriate patient selection worldwide. The reasons for low utilization of surgical LVRS are no doubt multifactorial but, of course, are significantly influenced by the attitudes of pulmonologists in relation to the procedure. I believe we should remain diligent in our efforts to educate physicians and the public regarding the risks and the benefits of LVRS so that appropriate candidates can be offered an opportunity to achieve an improved quality of life.

# Survey Checks Temp of Flu Prevention Efforts

*Experts support nearly universal vaccination for 2010-2011 season.*

BY HEIDI SPLETE  
*Elsevier Global Medical News*

WASHINGTON – Of 400 U.S. physicians surveyed online, 95% said they have received flu vaccinations for the 2010-2011 flu season or plan to do so, according to data collected by the National Foundation for Infectious Diseases.

These results are encouraging, because they show that more physicians are practicing what they preach about flu vaccination, said Dr. William Schaffner, president of the NFID, said at a press conference on influenza sponsored by the foundation.

"I am optimistic that we are becoming a culture of prevention," Dr. Schaffner said.

"Plenty of flu vaccine is anticipated for this year," along with a plentiful supply of antiviral medication, he emphasized, and vaccines are available at pharmacies as well as doctors' offices.

"Flu vaccination is the best way to protect yourself against the flu," said Dr. Thomas

Frieden, director of the Centers for Disease Control and Prevention. Every year thousands of Americans die from influenza, he said.

For the 2010-2011 flu season, the CDC recommends universal vaccination for everyone aged 6 months and older.

Several vaccination options are available, including a flu shot, a nasal spray, and a high-dose vaccine for older adults, Dr. Frieden said.

Dr. Daniel Jernigan, deputy director of the influenza division in the CDC's National Center for Immunization and Respiratory Diseases, said that this year's vaccine contains antibodies against three flu viruses: influenza B, influenza A (H3N2), and influenza A (H1N1).

Approximately 119 million doses of 2010-2011 flu vaccine already have been distributed in the United States, with a total of 160 million doses anticipated, Dr. Jernigan said.

There is no need for a separate H1N1 vaccine this year, he noted.



Approximately 119 million doses of 2010-2011 flu vaccine already have been distributed, Dr. Daniel Jernigan said.

So far this year, the H3N2 virus has been the most commonly seen, Dr. Jernigan said. While children were disproportionately affected by the 2009 H1N1 virus, "when H3N2 is dominant, we see more illness in children and older adults," he said.

Another important reason to vaccinate children is that they are incredibly efficient at spreading the flu – to their peers, family members, and other close contacts, said Dr. Judith S. Palfrey, past president of the American Academy of Pediatrics.

Dr. Palfrey said that children under 9 years of age who have never been vaccinated against the flu should receive two doses this year, given at about four weeks apart. One dose is sufficient for previously vaccinated children, she said. A complete algorithm for childhood vaccination is available at the American Academy of Pediatrics Web site.

More information about this year's influenza vaccine is available at the CDC's flu Web site [cdc.gov/flu](http://cdc.gov/flu).

Although influenza vaccination is recommended for most

individuals, some people should not receive the flu vaccine.

According to the CDC, individuals who are allergic to eggs or who have had a history of severe reaction to an influenza vaccination should not be vaccinated, nor should anyone who has developed Guillain-Barré syndrome within 6 weeks after receiving an influenza vaccine.

Those with a moderate to severe illness that includes a fever should wait until they recover before getting vaccinated.

And children younger than 6 months of age should not receive any type of flu vaccine.

The press conference was sponsored by the National Foundation for Infectious Diseases in partnership with the National Influenza Vaccine Summit.

The press conference was also supported in part by the Centers for Disease Control and Prevention and by unrestricted educational grants to the NFID from Flu Vaccine Business Practices Initiative (c/o HIDA), Genentech, GlaxoSmithKline, MedImmune, Merck and Co., Novartis Vaccines, Pfizer, Sanofi Pasteur, and Walgreens. ■

## Most Health Care Workers Skipped 2009 H1N1 Vaccine

BY BRUCE JANCIN  
*Elsevier Global Medical News*

VAIL, COLO. – Acceptance of the pandemic 2009 H1N1 influenza vaccine by U.S. health care workers was, in a word, "terrible," Dr. Adriana Weinberg declared.

A mere 37% of physicians and other health care workers were vaccinated against the pandemic virus, Dr. Weinberg reported at the annual conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

Uptake of the vaccine by two notably high-risk patient groups – pregnant women, and children and adolescents aged 6 months to 17 years – was equally poor at 38% and 37%, respectively, said Dr. Weinberg, professor of medicine, pediatrics, and pathology, and medical director of the clinical virology laboratory at the University of Colorado Hospital, also in Denver. These data were provided to the National Vaccine Advisory Committee by the Centers for Disease Control and Prevention.

Among parents and other care providers for infants less than 6 months of age, vaccine acceptance was even worse at 14%.

Moreover, only 25% of adults aged 24-64 years with immunosuppression or other chronic medical conditions placing them at elevated risk for increased flu morbidity got vaccinated. That was

**VITALS** **Major Finding:** Only 37% of physicians and other health care workers were vaccinated against the pandemic virus.

**Data Source:** CDC data provided to the National Vaccine Advisory Committee.

**Disclosures:** Dr. Weinberg disclosed serving as a consultant to MedImmune, Astellas, GlaxoSmithKline, and Merck.

essentially the same rate as in the overall U.S. population, including both high-priority and non-high-priority individuals.

As a result of this low uptake, many millions of soon-to-expire doses of pandemic 2009 H1N1 influenza monovalent vaccine are being destroyed.

In several studies, the main reason cited by health care workers and pregnant women for not accepting the vaccine was fear of side effects, especially Guillain-Barré syndrome, which was an issue with the 1976 swine flu vaccine. The safety concerns proved baseless this time around, as evidenced by consistently reassuring findings from three separate sources: the Vaccine Safety Datalink, the Vaccine Adverse Event Reporting System, and the Emerging Infections Program.

For example, there were no deaths and no cases of Guillain-Barré syndrome among recipients of 438,376 doses of the vaccine in managed care organizations

participating in the Vaccine Safety Datalink. And during surveillance for Guillain-Barré syndrome conducted through the Emerging Infections Program, the rate of cases was 1.92/100,000 person-years among vaccine recipients, compared with 1.21/100,000 person-years among nonrecipients.

That 0.7/100,000 person-years excess of Guillain-Barré syndrome associated with the pandemic H1N1 vaccine is similar to that associated with the seasonal influenza vaccine, according to Dr. Weinberg.

One audience member said the reason a lot more families in his practice didn't get vaccinated against H1N1 wasn't fear of side effects; it was that he and other office-based physicians in his community didn't get shipments of the vaccine until after the second and as it turned out, final, wave of the 2009 pandemic had passed.

Dr. Weinberg agreed that lack of timely vaccine availability caused by long delays in the cumbersome manufacturing process was a huge problem. A potential solution would be to produce influenza vaccines in cell culture instead of eggs, something the Food and Drug Administration is very reluctant to allow, although one such flu vaccine was recently approved in Europe. Another answer would be to identify common epitopes that confer cross-strain protection against all

influenza strains, so a new vaccine wouldn't have to be created in advance of every flu season.

"There has been a big push on this. There are some good candidate epitopes emerging in the last year. We shall see," the virologist said.

The vaccine being manufactured for the coming 2010-2011 flu season contains antigens for a pandemic 2009 H1N1 influenza virus as well as a seasonal influenza A H3N2 Perth 2009 virus and an influenza B Brisbane 2008 virus. The immunization schedule recommended by the CDC calls for a single dose of the vaccine for adults and children older than age 10 years. Children aged 6 months to 9 years are to receive two doses 21 days apart unless they are in the minority who received the pandemic H1N1 monovalent vaccine last season, in which case they are to get a single dose of the trivalent vaccine. Despite this recommendation, a recent randomized controlled trial concluded that a single dose may be sufficiently immunogenic in young children (*JAMA* 2010;303:37-46).

"We do anticipate circulation of the pandemic H1N1 strain in the next flu season, but I have to caution you that in the Southern Hemisphere, where influenza season is going on right now, there is very, very little pandemic H1N1. What predominates are the A H3N2 and the B Brisbane," she said. ■

# Surgeon General: Even One Cigarette Is Harmful

BY ALICIA AULT

*Elsevier Global Medical News*

WASHINGTON – For the first time, there is evidence of immediate and direct harm done by smoking even one cigarette, according to the 30th annual U.S. Surgeon General's Office report on smoking.

Surgeon General Regina M. Benjamin said at a press briefing that previous reports from her office honed in on the various diseases that smoking could cause. "This report focuses on how tobacco smoke causes damage to every organ in your body," she said.

When asked why this report could make a difference when so many previous warnings have not convinced all Americans to quit smoking, Dr. Benjamin said that she thinks that the direct evidence of harm will personalize the message.

The 700-page "Report of the Surgeon General: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease" determined that tobacco smoke contains 7,000 chemicals, hundreds of which are known to be toxic and 70 of which are carcinogenic, she noted.

The report describes multiple insults to the body from those chemicals, including changes in DNA that can lead to cancer; damage to the lining of the lungs; obstructive pulmonary disease and bronchitis; stress on the vasculature and cardiovascular disease; and an increased risk of heart attack, stroke, and aortic aneurysm.

Smoking also interferes with the effectiveness of chemotherapy and the control of blood sugar and leads to fertility problems, including difficulty conceiving, miscarriage, and preterm birth. Just one

cigarette can trigger a heart attack or stroke, she said.

In addition, the report examined the effects of secondhand smoke, finding that even brief exposure can cause cardiovascular disease and can also trigger acute cardiac events, such as heart attack. Babies exposed to secondhand smoke are more likely to die of sudden infant death syndrome.

The report highlights the increasingly addictive properties of today's cigarettes, many of which are designed to enhance nicotine absorption and its crossing of the blood-brain barrier, Dr. Benjamin said.

Department of Health and Human Services Secretary Kathleen Sebelius said at the briefing that the report shows that "there is no safe level of exposure to tobacco smoke," and, she added, "if you're a smoker, the best time to quit is right now."

John R. Seffrin, Ph.D., CEO of the American Cancer Society Cancer Action Network, agreed. "Today's report makes it clear, once again, that there is no such thing as a safe cigarette and no such thing as a safe level of exposure to secondhand smoke for nonsmokers," he said in a statement.

Ms. Sebelius noted that, every day, 4,000 Americans under 18 years old try their first cigarette, and 1,000 become daily smokers. Some 1,200 Americans die every day as a result of tobacco-related causes, she said, and the report is part of the Obama administration's ongoing strategy to completely eliminate tobacco use.

The Surgeon General's report is available at [www.surgeongeneral.gov](http://www.surgeongeneral.gov). The office has also created a consumer-friendly version of the report and a printable, one-page fact sheet for physicians to use in discussing the report with their patients. ■

COMMENTARY

**Dr. Philip Marcus, FCCP, comments:** In 1964, the first Surgeon General's report on the effects of smoking on health was released. In the next 46 years, extensive data from thousands of studies have consistently substantiated the devastating effects of smoking on the lives of millions of Americans and others around the world. Yet today in the United States, tobacco use remains the single largest preventable cause of death and disease for both men and women.



Now, this 2010 report of the Surgeon General explains beyond a shadow of a doubt how tobacco smoke causes disease, essentially validating earlier findings, and expands and strengthens the science behind these findings. Armed with this irrefutable data, the time has come to mount a full-scale assault on the tobacco epidemic.

More than 1,000 people are killed every day by cigarettes, and one-half of all long-term smokers are killed by smoking-related diseases. This report should lay the issue to rest at this time, and hopefully there can be a true reduction in cigarette smoking and a concomitant end to the epidemic of smoking-related illnesses.

observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose [see *Dosage and Administration* (2.2)].

#### 8.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

#### 8.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment [see *Clinical Pharmacology* (12.3)].

## 10 OVERDOSAGE

### 10.1 Signs and Symptoms

**DULERA:** DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

**Mometasone Furoate:** Chronic overdosage may result in signs/symptoms of hypercorticism [see *Warnings and Precautions* (5.7)]. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

**Formoterol Fumarate:** The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m<sup>2</sup> basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

### 10.2 Treatment

**DULERA:** Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

Manufactured by 3M Health Care Ltd.,  
Loughborough, United Kingdom.  
Manufactured for Schering Corporation, a subsidiary of



**MERCK & CO., INC.**

Whitehouse Station, NJ 08889 USA.

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# H1N1 Isn't Over

Threat • from page 1

least 90% of the population were vaccinated, herd immunity would protect even those people who can't be vaccinated, such as infants under 6 months of age and others with contraindications, Dr. Harrison said.

Given last year's experience, that's not likely to happen. U.S. health officials hoped to have enough antigen for 229 million doses. In the end, only 162 million doses were produced, and despite widespread publicity about the danger of H1N1, only 94 million doses were used, he said. "Everyone wanted the vaccine in August, and no one wanted it in December."

The reason the pandemic didn't kill as many people as feared may have been that elderly people, normally the most at risk, had some residual immunity from a swine flu outbreak in the 1960s and a vaccine used at that time, Dr. Harrison said.

Vaccination of children is particularly important because so many attend schools and day care facilities, where they play a key role in spreading the virus. Very young children are particularly vulnerable, with hospitalization rates comparable to those of the elderly.

While results from studies have varied, combining



their data suggests the vaccine confers about a 68% immunity rate in children, Dr. Harrison said.

The vaccine is available in two forms: trivalent, inactivated influenza vaccine (TIV) and live, attenuated influenza vaccine (LAIV). The TIV vaccine is an intramuscular injection of killed viruses. It can be given to anyone over 6 months of age who is not allergic to the vaccine. Egg allergies are no longer considered an absolute contraindication, Dr. Harrison said, but the vaccine should be given to people with egg allergies only if an allergist is present. "I don't know how practical that is," he said.

LAIV is administered via an intranasal spray. Most people aged 2-49 years can get the vaccine this way, with the exception of children under 5 years of age with reactive airways diseases such as asthma, anyone with a high-risk medical condition, and pregnant women.

Unlike last year, when two vaccines were offered, one for seasonal flu and one for H1N1, this year one vaccine will protect against three strains:

- ▶ A/California/7/2009 (H1N1), which caused last season's pandemic.
- ▶ B/Brisbane/60/2008, the same seasonal strain from last season, which is already prevalent in the Southern Hemisphere.

▶ A/Perth/16/2009 (H3N1), a new strain already detected in Iowa.

Most children aged 6 months to 8 years should receive two doses of the vaccine, Dr. Harrison said. Children who received one or two H1N1 2009 pandemic vaccinations in 2009-2010 and two doses of seasonal vaccine, or who were vaccinated prior to 2009-2010 and also got at least one H1N1 2009 pandemic dose in 2009-2010, need only one vaccination this season, according to the Centers for Disease Control and Prevention guidelines.

For those children who do get influenza, antiviral drugs are available. The 2009 H1N1 pandemic strain and H3N2 are almost completely resistant to adamantanes, but have little or no resistance to oseltamivir or zanamivir.

When commercially manufactured Tamiflu Oral Suspension (12 mg/mL) is not available, it is possible to compound Tamiflu (oseltamivir) 75-mg capsules to suspension for children. Instructions are available on the Food and Drug Administration Web site at [www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm147992.pdf](http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm147992.pdf).

How do physicians know when to use an antiviral? Rapid tests for H1N1 work this season – unlike last season, Dr. Harrison said.

Dr. Harrison disclosed a financial relationship with GlaxoSmithKline Vaccine Group. ■

## COMMENTARY

**Dr. Burt Lesnick, FCCP, comments:** At press time, my home state of Georgia is the only state with epidemic influenza, although it is mainly influenza B. Clinicians are advised to keep abreast of their local virology and respond accordingly.

## Avoid Afluria Flu Vaccine in Children Under 9 Years

BY ROBERT FINN

Elsevier Global Medical News

The Advisory Committee on Immunization Practices voted to recommend that a seasonal influenza vaccine manufactured by CSL Biotherapies for the U.S. market not be used in children between the ages of 6 months and 8 years.

The company's trivalent influenza vaccine (TIV) sold under the trade name Afluria in the United States was associated with a large increase in the risk of fevers and febrile seizures in children in Australia and New Zealand. In April 2010, authorities in those two countries

**CHILDREN AGED 5-8 YEARS CAN RECEIVE THE CSL VACCINE IF THEY ARE AT ESPECIALLY HIGH RISK FROM INFLUENZA AND NO OTHER VACCINE IS AVAILABLE.**

recommended that physicians suspend use of CSL's influenza vaccines in children aged 5 years and under. In response, the company voluntarily withdrew its vaccine from markets in the southern hemisphere.

In the northern hemisphere, CSL's influenza vaccines have been approved for use in Germany, the United Kingdom, and the United States. In June 2010, authorities in the United Kingdom recommended that physicians avoid using CSL's influenza vaccine in children aged 5 and under.

In making their recommendation, members of the Centers for Disease Control and Prevention's Advisory

Committee on Immunization Practices (ACIP) noted that there should be adequate supplies of seasonal influenza vaccine even in the absence of Afluria. Other manufacturers are expected to supply 145-150 million doses of the vaccine in the United States; the largest number of doses ever used in one flu season was 114 million.

During the course of a teleconference sponsored by ACIP, representatives of Sanofi-Aventis, GlaxoSmithKline, Novartis, and MedImmune all said that they had adequate supplies of vaccine, and they were willing to increase production if necessary to compensate for the 6-12 million doses that CSL had been expected to provide.

According to the CDC's medical epidemiologist Dr. Tim Uyeki, CSL's vaccine was associated with a ninefold increase in the risk of febrile seizures, compared with other manufacturers' vaccines in children aged 6 months through 4 years in Australia. The rate was nine per 1,000 doses in these children, compared with an expected rate of one per 1,000 doses. The rate of febrile seizures was especially high in children aged 3-4 years given Fluvax Junior, one of CSL's two versions of this year's TIV. The rate in those children was 15 per 1,000 doses.

Febrile seizures occurred an average of 7.2 hours after the child received a dose of vaccine, with a range of 5.9-8.4 hours. Dr. Uyeki said that no explanation for the increased risk of fever and febrile seizures has been identified.

Although there was no apparent increase in febrile seizures in children aged 5-8 years, children in that age group did experience an increase in the incidence of fever. Sixteen percent of children in that

age group experienced a fever following a dose of a CSL flu vaccine, compared with 9% of children receiving another manufacturer's vaccine.

ACIP members voted to include children aged 5-8 years in their recommendation in order to increase the simplicity and consistency of the public health message. Other ACIP recommendations regarding flu vaccination in children, both for the seasonal TIV and for pandemic influenza A(H1N1), involve children age 6 months to 8 years, and most members believed it would be confusing to have this new recommendation cover children age 6 months to 5 years.

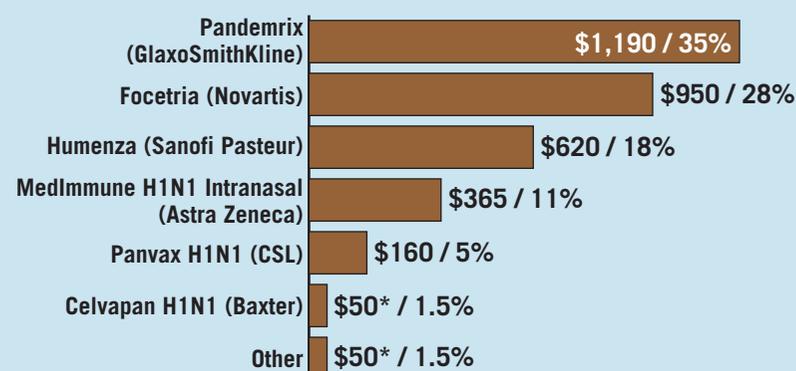
They did agree, however, that children aged 5-8 years could receive the CSL vaccine if they were at especially high risk from influenza and if no other vaccine was available.

Several committee members voiced concern about providers who may already have placed orders for the CSL vaccine. Since most vaccine from other manufacturers has already been allocated, they worried that it would be too late for some clinicians to change their orders. In response, a representative from the American Medical Association recommended that providers visit the AMA's Influenza Vaccine Availability Tracking System (IVATS) at [www.preventinfluenza.org/ivats](http://www.preventinfluenza.org/ivats). A spreadsheet at that site lists names and contact information for distributors who have vaccine available.

While several members of ACIP disclosed that they had relationships with vaccine manufacturers, only members with no such conflicts of interest were permitted to vote. ■

## DATA WATCH

### World H1N1 Flu Vaccine Sales, 2009 (in millions/market share)



\*Estimated

Note: Based on annual reports of vaccine concerns, trade media coverage, company Web sites, and medical and government literature.

Source: Kalorama Information

# Did you know REVATIO samples are just a phone call away?

## Order REVATIO Starter Samples by phone

Contact the REVATIO Sample Fulfillment  
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### Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

### Important Safety Information

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with  $\alpha$ -blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

**Revatio**<sup>®</sup>  
sildenafil  
20 mg tablets  
**Start With Confidence**<sup>™</sup>

Please see Brief Summary of Prescribing Information on the following pages.

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

# Live, Inactivated Flu Vaccines Equally Cost Effective

BY MARY ANN MOON  
Elsevier Global Medical News

Despite recent reports that the intranasal live attenuated influenza vaccine might cause more adverse events in young children than does the inactivated influenza vaccine, the cost-effectiveness of the two approaches remains comparable, according to a recent study.

In a mathematical simulation model,

both the live attenuated vaccine and the inactivated vaccine yielded similar cost-effectiveness ratios of less than \$40,000 per quality-adjusted life year (QALY) among children under 5 years, which compares well with other well-accepted pediatric interventions, said Lisa A. Prosser, Ph.D., of the University of Michigan Health System, Ann Arbor, and her associates (Arch. Pediatr. Adolesc. Med. 2010 [doi:10.1001/archpediatrics.2010.182]).

The investigators assessed the cost-

effectiveness of each of the vaccines and of no vaccination using a mathematical simulation model that estimated the effects on influenza-related health outcomes in a hypothetical cohort of healthy children aged 6 months to 4 years.

The live attenuated vaccine was projected to avert more influenza episodes, influenza-related hospitalizations, and deaths than was the inactivated vaccine. However, this benefit was somewhat counterbalanced by an increase in adverse

events with the live attenuated vaccine.

Under different conditions, the model showed that cost-effectiveness ratios ranged from \$20,000/QALY to \$33,000/QALY with the live attenuated vaccine and \$21,000/QALY to \$37,000/QALY with the inactivated vaccine.

This study was funded by the Centers for Disease Control and Prevention through the Harvard/CDC Joint Initiative in Vaccine Economics. No financial conflicts of interest were reported. ■

## REVATIO® (SILDENAFIL)

### Brief Summary of Prescribing Information

**INDICATIONS AND USAGE:** REVATIO® is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

### Limitation of Use

The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

### DOSAGE AND ADMINISTRATION

#### Pulmonary Arterial Hypertension (PAH)

##### REVATIO Tablets

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

##### REVATIO Injection

REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.

The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight.

A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

### CONTRAINDICATIONS

#### Use with Organic Nitrates

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

#### Hypersensitivity Reactions

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reaction. The majority of reported events were non-serious hypersensitivity reactions.

### WARNINGS AND PRECAUTIONS

#### Cardiovascular Effects

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with resting hypotension [BP < 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution for:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP > 170/110);
- Patients currently on bosentan therapy.

#### Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported [see Drug Interactions]. No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

#### Effects on Bleeding

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

#### Use with Ritonavir and Other Potent CYP3A Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A inhibitors with REVATIO is not recommended.

### Effects on the Eye

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors [see Adverse Reactions].

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

### Hearing Impairment

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [see Adverse Reactions].

### Combination with other PDE5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

### Prolonged Erection

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

### ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension [see Warnings and Precautions]
- Vision loss [see Warnings and Precautions]
- Hearing loss [see Warnings and Precautions]
- Priapism [see Warnings and Precautions]

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

**Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent (> 1%) than Placebo**

ADVERSE EVENTS %	Placebo (n=70)	Revatio 20 mg TID (n=69)	Placebo-Subtracted
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis nos	0	4	4
Diarrhea nos	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis nos	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

nos: Not otherwise specified

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

# Infant Vaccinations Met Goals of Healthy People 2010

BY DAMIAN McNAMARA  
Elsevier Global Medical News

ATLANTA – Vaccination of U.S. infants 19-35 months of age remains high at 90% or greater for routine immunizations, according to results of the 2009 National Immunization Survey released by the Centers for Disease Control and Prevention.

This means vaccine coverage in

2009 met or exceeded the 90% goal set by the national Healthy People 2010 initiative.

This survey of vaccinations for 17,313 children nationwide revealed that less than 1% of young children born between January 2006 and July 2008 received no vaccinations (MMWR 2010;59:1171-7).

“Today’s report is generally very reassuring, despite concerns we’ve seen in the past about whether

parents are continuing to have their children vaccinated, and despite some resurgences in vaccine-preventable diseases in particular areas,” Dr. Anne Schuchat, director of the National Center for Immunization and Respiratory Diseases at the CDC, said during a telebriefing.

Some substantial variation in vaccine coverage between states was again revealed by this annual survey, suggesting that there is still work to be done in some communities.

Dr. Schuchat addressed the outbreak of pertussis cases in California, responsible for nine infant deaths since January 2010. The coverage in California for four doses of DTaP, the pertussis-containing shot for babies, was 83%, according to state records. “We don’t think it’s the coverage level in babies and toddlers that is leading to that pertussis challenge in California.” Instead, “we think the challenge with those pertussis cases is the increasing vaccination of teens and adults,” she said, although “it continues to be important for babies and toddlers to get their DTaP doses.”

The CDC strongly recommends everyone aged 11 years and older, particularly new parents and those in close contact with young children, receive the vaccination against pertussis. Dr. Schuchat said, “The situation in California is serious, and we are working together with the California health department to really promote uptake of the pertussis vaccine for teens and adults.”

The survey showed national coverage for MMR vaccinations experienced “a significant but not large” drop from 92% in 2008 to 90% in 2009. “That might be a warning sign of larger drops to come or a small change that, because our survey is so large, was statistically significant,” Dr. Schuchat said. Even though national coverage numbers are 90%, “you can still have large pockets of susceptible children.”

“Those two examples [pertussis and measles] show that we cannot let our guard down,” Dr. Schuchat said.

The survey also revealed a substantial drop in coverage for one vaccine, *Haemophilus influenzae* B (Hib). A total of 84% of children aged 19-35 months received the three recommended doses in the survey. This represents a decrease of more than 6 percentage points vs. 2008 that “really just reflects the national shortage” of this vaccine between December 2007 and September 2009, Dr. Schuchat said. She commended clinicians for following recommendations to drop the booster shot during this shortage, and added that the vaccine is now readily available.

Other survey findings indicate that 44% of children received full coverage for the rotavirus vaccine during infancy. This is the first national survey data to report adoption of the rotavirus vaccine since its U.S. licensure in 2006. “That is really good uptake of this vaccine. Of course, we’re already seeing a very important drop in disease caused by the rotavirus,” Dr. Schuchat said. ■

VITALS

**Major Finding:** Vaccination coverage remained at 90% or greater for most routine vaccines administered to children 19-35 months of age in the United States in 2009.

**Data Source:** The 2009 National Immunization Survey of U.S. households, with reports verified for 17,313 children whose providers provided vaccination records.

**Disclosures:** Dr. Schuchat had no relevant disclosures.

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>6% difference) are shown in Table 2.

**Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo**

ADVERSE EVENTS %	Placebo Epoprostenol (n = 131)	Revatio Epoprostenol (n = 134)	Placebo-Subtracted %
Headache	34	57	23
Edema <sup>^</sup>	13	25	14
Dyspepsia	2	16	14
Pain in extremity	6	17	11
Diarrhea	18	25	7
Nausea	18	25	7
Nasal congestion	2	9	7

<sup>^</sup>includes peripheral edema

**REVATIO Injection**

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

**Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Cardiovascular Events**

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

**Decreases in and Loss of Vision**

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [see Warnings and Precautions].

**Loss of Hearing**

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors [see Warnings and Precautions].

**Other Events**

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

**DRUG INTERACTIONS**

**Nitrates**

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

**Ritonavir and other Potent CYP3A Inhibitors**

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended [see Warnings and Precautions].

**Alpha-blockers**

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

**Amlodipine**

When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Category B**

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m<sup>2</sup> basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m<sup>2</sup> basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery**

The safety and efficacy of REVATIO during labor and delivery has not been studied.

**Nursing Mothers**

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

**Geriatric Use**

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Hepatic Impairment**

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

**Renal Impairment**

No dose adjustment is required (including severe impairment Cl<sub>CR</sub> < 30 mL/min).

**OVERDOSAGE**

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TID. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m<sup>2</sup> basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

**PATIENT COUNSELING INFORMATION**

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.
- Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

**RX only**

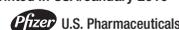
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## CHEST Physician Editorial Advisory Board Gains New Members and a Deputy Editor

**Dr Stuart M. Garay, FCCP**, is a practicing pulmonologist and Clinical Professor of Medicine at the New York University School of Medicine. He is President of University Physicians Network, a physician founded, owned, and operated organization that is committed to helping member physicians cope with the changes and challenges of the health-care business environment. Dr Garay is a member of the Practice Operations NetWork Steering Committee. In the past, he has served on the ACCP Board of Regents as a Regent at Large; as a member of the CHEST scientific program committee; and on the steering committee of the Clinical Pulmonary Medicine NetWork. Dr Garay's clinical and research interests include airway diseases ranging from asthma to bronchiectasis, mycobacterial infections, and sleep apnea.



DR STUART M. GARAY, FCCP

He has participated in numerous clinical trials for asthma and COPD, and he has published more than 50 papers and chapters on various topics in pulmonary medicine. He is co-editor of a text, *Tuberculosis*.

**Dr Darcy D. Marciniuk, FCCP**, is a Professor of Medicine and Head of the Division of Respiratory, Critical Care, and Sleep Medicine at the University of Saskatchewan, Saskatoon, SK, Canada. Dr Marciniuk received his Doctor of Medicine from the University of Saskatchewan and had specialty training in internal medicine and respiratory medicine at the University of Western Ontario and at the University of Manitoba. He returned to Saskatoon in 1990, where he assumed his current faculty position with the University of Saskatchewan.



DR DARCY D. MARCINIUK, FCCP

Dr Marciniuk is currently President-Designate of the ACCP, a member of the ACCP Board of Regents, and a Trustee of The CHEST Foundation. He has held a number of leadership positions in the ACCP, including Governor of Saskatchewan; Chair of the Pulmonary Physiology, Function, and Rehabilitation NetWork; and Co-Chair of CHEST 2005. Dr Marciniuk is Past Chair of the Royal College of Physicians and Surgeons of Canada Examination Committee in Respiratory and is a Past President of the Canadian Thoracic Society. He has published more than 90 peer-reviewed publications, chapters, and reviews. His interests in pulmonary medicine include COPD and clinical physiology and exercise.

**Dr Marcos I. Restrepo, MSc, FCCP**, is an Assistant Professor of Medicine in the Division of Pulmonary/Critical Care Medicine at the University of Texas Health Science Center at San Antonio. He is the Director at the Medical Intensive Care Unit at the South Texas Veterans Health Care System, Audie L. Murphy Division. He completed his residency in internal medicine and fellowships in infectious diseases, pulmonary disease, and critical care medicine at the University of Texas Health Science Center



DR MARCOS I. RESTREPO, MSC, FCCP

at San Antonio. Dr Restrepo is an investigator for VERDICT, which aims to translate medical evidence into clinical practice. He has been an author or co-author of more than 60 journal articles and 7 book chapters and has lectured nationally and internationally. Dr Restrepo serves on the ACCP Respiratory Care NetWork Steering Committee and previously was on the Chest Infections NetWork Steering Committee. He serves as a reviewer for 14 journals, including *CHEST*, *Critical Care Medicine*, and *American Journal of Respiratory and Critical Care Medicine*. Dr Restrepo's primary research interests include immunomodulation in sepsis and pneumonia, appropriate application of interventions to prevent and treat critically ill patients with severe infections, and improving health outcomes and quality of care of patients in the ICU with pneumonia and sepsis.

**Dr W. Michael Alberts, FCCP**,

has agreed to assume the Deputy Editor in Chief role for *CHEST Physician* and work with Dr Selecky during the final year of his term in 2011. Dr Alberts will then take over as Editor in Chief from 2012 through 2015. We thank Dr Alberts for his continued leadership service to *CHEST Physician*.



DR W. MICHAEL ALBERTS, FCCP

### CELEBRATION OF PEDIATRIC PULMONOLOGY 2011

April 8-10  
Ft. Lauderdale, Florida

Co-Chairs  
LeRoy M. Graham, MD, FCCP  
Dennis Gurwitz, MBBCh, FAAP

Don't miss this state-of-the-art update in clinical pediatric pulmonology, featuring the latest research in pulmonology, sleep, pulmonary-GI disorders, and surgery. The course will combine plenary-style lectures, question and answer sessions, interactive small group workshops, and case presentations, allowing attendees to benefit from a wide variety of learning methods. Many sessions will be interactive, so you can address specific issues that impact your practice.

**Who Should Attend**  
Pediatric Pulmonologists  
General Pediatricians  
Family Physicians  
Pediatric Intensivists  
Allergists  
Pediatric Nurse Practitioners  
Respiratory Therapists

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### CHEST Goes Mobile on iPhone®, iPod touch®, and iPad®

Among the most trusted sources for cutting-edge original research in the multi-disciplinary specialties of chest medicine, the *CHEST* journal is now available as an app for the iPhone®, iPod touch®, and iPad®.

The *CHEST* Journal App allows readers to browse the tables of contents from the three most recent issues and papers in press, view abstracts, and—during the free-trial period, lasting until June 2011—read full-text articles.\*

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The *CHEST* Journal App can be downloaded by searching "CHEST Journal" in the App Store<sup>SM</sup> or on iTunes®.

\*After the free-trial period expires, full-text content will be made available to subscribers through a one-time log-in.

### January Lessons

► Prescription Opiate/Opioid Drug Abuse: A New Epidemic.

By Susan Y. Kim-Katz, PharmD; and Ilene B. Anderson, PharmD

**PCCSU**  
PULMONARY, CRITICAL CARE, SLEEP UPDATE

► Respiratory Manifestations of Gastroesophageal Reflux.

By Lindsey B. Roenigk, MD; and Susan M.

Harding, MD, FCCP

[www.chestnet.org/accp/pccsu](http://www.chestnet.org/accp/pccsu)

## Guidelines Moving Forward

In ongoing efforts to strengthen its internationally recognized guideline development, publication, and dissemination, the ACCP has hired two new employees with notable backgrounds contributive toward this end.

Rebecca Diekemper, MPH, comes to the ACCP from BJC HealthCare in St Louis, where she served as a clinical epidemiologist. In addition to reviewing guidelines and the primary evidence, Rebecca has performed some systematic reviews and developed a tool to assess systematic reviews, which has been compared to the Guyatt-Oxman and other such tools. She will be primarily working on the lung cancer guidelines, managing the Policy and Procedures Subcommittee, and assisting with the full HSP Committee.

Joe Ornelas, DC, MS, MA, is working toward completing a PhD in health policy and administration at the University of Illinois School of Public Health. In various jobs in academic and hospital settings, he has conducted extensive literature reviews, performed probability-based decision analyses for cost-effectiveness and cost-utility evaluations, and worked on many projects requiring data management and analysis. Joe will work primarily on the antithrombotic and immunosuppressives guidelines and will manage the HSP Guidelines Subcommittee. ■

## New HHS/CCSC Awards Program Announced

Reducing the incidence of healthcare-associated infections (HAIs) is a priority for the ACCP. A new national awards program, Achievements in Eliminating Healthcare-Associated Infections, cosponsored by the US Department of Health and Human Services (HHS) and the Critical Care Societies Collaborative (CCSC), will annually recognize teams of critical care professionals and health-care institutions

that achieve excellence and notable, sustained improvements in preventing HAIs, specifically infections involving critical care. The awards program intends to motivate the health-care community to achieve wide-scale reduction and elimination of HAIs and further motivate other clinicians, hospital executives, and facilities to improve clinical practice through utilization of evidence-based guidelines. The ACCP actively participates

in the CCSC, along with the American Association of Critical-Care Nurses, American Thoracic Society, and Society of Critical Care Medicine.

The initial phase of the awards program will emphasize success related to reducing and eliminating central line-associated bloodstream infections and ventilator-associated pneumonia. Applications are due January 29, 2011. For questions, contact [awards@aacn.org](mailto:awards@aacn.org). ■

## This Month in CHEST: Editor's Picks

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

► **Effects of Bronchoconstriction, Minute Ventilation, and Deep Inspiration on the Composition of Exhaled Breath Condensate.**

By Dr J. S. Debley et al.

► **Interpreting Lung Function Data Using 80% Predicted and Fixed Thresholds Misclassifies More Than 20% of Patients.**

By Dr M. R. Miller et al.

► **Factors at Admission Associated With Bleeding Risk in Medical Patients: Findings From the**

**IMPROVE Investigators.**

By Dr H. Decousus et al.

► **Beneficial Effects of Treatment With Anti-IgE Antibodies (Omalizumab) in a Patient With Severe Asthma and Negative Skin-Prick Test Results.**

By Dr M. van den Berge et al.

SPECIAL FEATURE

► **Seventh Edition of the Cancer Staging Manual and Stage Grouping of Lung Cancer: Quick Reference Chart and Diagrams.**

By Dr O. Lababede et al.



EDITORIALS

► **Developing Complementary Clinical Guidelines for Pulmonary Rehabilitation in COPD: Why Add More?** By Dr R. Goldstein; and Dr D. Marciniuk.

► **The Journal and 2011:**

**A Time for Stocktaking.** By Dr R. S. Irwin; and N. Augustyn.

TRANSLATING BASIC RESEARCH INTO CLINICAL PRACTICE

► **Systemic Manifestations of COPD.** By Dr Y. Nussbaumer-Ochsner; and Dr K. F. Rabe.

AMERICAN COLLEGE OF CHEST PHYSICIANS

# 2011 Education Calendar

**Sleep Medicine 2011**

January 27-30  
Tempe, AZ

**Celebration of Pediatric Pulmonology 2011**

April 8-10  
Ft. Lauderdale, FL

**ACCP Critical Care Medicine Board Review 2011**

August 26-30  
San Antonio, TX

**ACCP Sleep Medicine Board Review 2011**

August 26-29  
San Antonio, TX

**Lung Pathology 2011**

August 30  
San Antonio, TX

**Mechanical Ventilation 2011**

August 30  
San Antonio, TX

**ABIM Critical Care Medicine and Pulmonary Disease SEP Modules**

August 30  
San Antonio, TX

**ACCP Pulmonary Medicine Board Review 2011**

August 31-September 4  
San Antonio, TX

**CHEST 2011**

October 22-27  
Honolulu, Hawaii

**ACCP Simulation Program for Advanced Clinical Education**

**Basic and Advanced Bronchoscopy Skills**

February 11-13  
Orlando, FL

August 5-7  
Chicago, IL

**Mechanical Ventilation**

February 25-27  
Chicago, IL

**Difficult Airway Management**

March 18-20  
July 22-24  
Northbrook, IL

**Ultrasonography: Fundamentals in Critical Care**

April 15-17  
Baltimore, MD

**Focused Pleural and Vascular Ultrasound**

September 22-23  
Chicago, IL

**Critical Care Echocardiography**

September 24-25  
Chicago, IL

## NETWORKS

## Sepsis, Acute Kidney Injury, Sleep Disorders, Flu

## Critical Care

*The Kansas Sepsis Project*

Severe sepsis is a common cause of mortality, representing the most common cause of death in noncoronary ICUs (Bone et al. *Chest*. 1992;101[6]:1644). Sepsis is rapidly increasing in incidence, projected to affect over 1,000,000 patients per year in the United States by 2020 (Angus et al. *Crit Care Med*. 2001;29[7]:1303-1310). Rural patients develop severe sepsis in similar proportion to urban patients, yet access to critical care services in rural areas is limited.

Telemedicine can help to bridge the gap between the mostly urban supply of intensivists and underserved rural patients and their local physicians (Marcin et al. *J Pediatr*. 2004;144[3]:375). Various techniques have been utilized to address this need, ranging from video consultation to teleICU, with reasonable evidence that such care is comparable to hands-on ICU care (Hersh et al. *BMC Medical Informatics and Decision Making*. 2001;1:5). To further explore uses of telemedicine in the specialty of critical care medicine, a CME/performance improvement project dealing with improving care of patients with sepsis in rural Kansas was implemented via the Eli Lilly Distinguished Scholar Award of The CHEST Foundation. An objective of the project is to empower rural physicians to appropriately care for their own patients with sepsis, as an alternative to real-time telemedicine consultation.

The Kansas Sepsis Project brings CME and performance improvement to rural Kansas areas via telemedicine in both educational and advisory roles. The project provides a novel method for rural medical practitioners to obtain CME credit while performing sepsis quality improvement projects that are eligible for maintenance of board certification. The overall goal of the project is to demonstrate a statewide reduction in sepsis mortality through widespread provider participation, paving the way for similar projects in other rural states.

Dr Lucas R. Pitts, and  
Dr Steven Q. Simpson, FCCP,  
NetWork Vice-Chair and Third Eli Lilly  
and Company Distinguished Scholar in  
Critical Care Medicine

## Cardiovascular Medicine and Surgery

*Risk of Acute Kidney Injury With Same Admission Cardiac Catheterization and Cardiac Surgery*

Acute kidney injury (AKI) after open cardiac operations is associated with increased morbidity and short-term and long-term mortality. Prevention of AKI during and after surgery is of paramount importance. The Acute Kidney Injury Network definition of AKI is a 0.3 mg/dL or 50% increase in baseline creatinine value. It is common practice to provide diagnostic cardiac catheterization and cardiac surgery in the same admission. This practice may lead to a

higher risk of AKI with attendant increased risks for a higher morbidity and mortality. The question, therefore, remains as to the optimal timing of cardiac surgery following cardiac catheterization. A recent prospective study from the Northern New England Cardiovascular Disease Study Group looked at the incidence of AKI after cardiac catheterization in 668 patients undergoing non-emergent cardiac surgery during the same hospital admission (367 patients) or a later admission (301 patients) (Kramer et al. *Ann Thorac Surg*. 2010; 90[5]:1418).

The incidence of AKI was 50.2% in the same admission group vs 33.7% for the later admission group. The difference was highly significant ( $P=.009$ ). Patients undergoing surgery at a later admission had a 45% reduction in AKI. The authors concluded that "it is safe and possibly beneficial in terms of renal protection, to send patients home after cardiac catheterization with a plan for surgery during subsequent admission."

Dr G. Hossein Almassi, FCCP  
NetWork Vice-Chair

## Allied Health

*Sleep Disorders Specialty Exam Accredited*

The National Board for Respiratory Care (NBRC) invested several years developing an examination for respiratory therapists specializing in sleep disorders and therapeutic intervention. Candidates must be credentialed respiratory therapists with clinical experience in the testing, monitoring, diagnosis, and treatment of patients with sleep disorders. Successful candidates receive either the CRT-SDS or RRT-SDS federally trademarked credential designation depending on whether they attempted the examination as a CRT or an RRT.

The specialty examination was developed in accordance with stringent psychometric and other standards put forth by the National Commission for Certifying Agencies. This body also accredits the registered polysomnographic technologist (RPSGT) examination offered by the Board of Registered Polysomnographic Technologists (BRPT). Both the RPSGT and sleep disorders specialty (SDS) examinations were developed based on job content identified by national job analysis research.

Test specifications for the NBRC's SDS examination can be reviewed and printed by accessing the NBRC Web site at [nbrc.org](http://nbrc.org) and clicking on the "Examinations" tab. An online, full-length, free practice examination is also available.

The new specialty examination was developed in response to requests from

the NBRC's sponsors. The Board of Trustees is pleased to announce the new examination was recently accredited by the National Commission for Certifying Agencies (NCCA), continuing a long tradition of NCCA accreditation for all of the NBRC's credentialing programs. The NBRC was one of the first four organizations to have its examina-

tions accredited in 1977 when the NCCA was formed, and it is the only organization to continuously maintain accreditation of its credentialing programs for more than 30 years.

Gary A. Smith, CRT,  
FAARC  
NetWork Steering  
Committee Member

## Chest Infections

*Influenza: Brief Comments on the Recent 2009 Influenza A(H1N1) Epidemic and Observations on Vaccine*

Sporadic outbreaks of highly virulent avian H5N1 influenza and the recent outbreak of a pandemic A(H1N1) virus have heightened concerns about the eventual emergence of a particularly deadly pandemic virus. Influenza A virus represents one of the most prominent viral pathogens of modern times. Infection with this microbe results in an estimated 36,000 deaths<sup>1</sup> and over 200,000 hospitalizations<sup>2</sup> in the United States annually, with a projected total economic burden in excess of 80 billion US dollars per year.<sup>3</sup> According to the Centers for Disease Control and Prevention, the incidence of influenza virus infection in the US population may reach 20% during a typical flu season; however, this figure can increase substantially during periods of pandemic influenza. Although influenza is typically a self-limiting disease, serious complications can occur, including primary viral pneumonia, secondary bacterial pneumonia, myositis, and neurologic syndromes. The risk of mortality and disease complications is elevated for certain populations, including the young, old, immunosuppressed, and immunocompromised. During the most recent pandemic, infection/disease was witnessed in unique populations, such as pregnant women and children, with substantial mortality observed. Elderly individuals were not as predisposed, reflecting previous serologic evidence of prior exposure to similar influenza virus strains. The epidemic demonstrated differences in treatment efficacy for drugs; potential utilities of intensive support, including alternate ventilatory modes such as extracorporeal membrane oxygenation; and difficulties in administering and allocating resources. Interactions among physicians, health-care delivery systems, and administrations were stressed. The ability of influenza A virus to infect millions of people each year speaks to

the resilient nature of this pathogen and to the necessity for developing improved methods of disease prevention and treatment.

Although commercial influenza vaccines have been available since the mid-1900s, a number of key challenges continue to limit the efficacy of these vaccines. The rapid mutation rate of immunodominant glycoproteins on the virus surface necessitates annual revision of the vaccine and requires a broad network of laboratories to cooperatively perform surveillance on circulating influenza virus strains throughout the year. Importantly, current strain-specific vaccines are only 30% to 50% effective in preventing hospitalization and pneumonia in the elderly and are about 70% effective in preventing illness in healthy adults. Most recently (late 2010), several groups have observed disturbing trends of mistrust of vaccine formulations (individual components), which have resulted in refusal of vaccination by health-care persons of all types, including physicians and nurses.

Despite the extensive variability in strains of seasonal influenza, some research investigations have indicated the potential for developing universally protective immune responses against influenza viruses. Over the past decade, an array of conserved influenza virus epitopes have been identified, and the ability of both cell-mediated immune components and humoral immune components to elicit cross-protective immunity to heterologous influenza A viruses have been documented. Moreover, the improvement of influenza vaccine immunogenicity via inclusion of molecular adjuvants and modification of vaccine modality has been widely reported but rarely within the context of a universal influenza vaccine. Development of a maximally efficacious vaccine in primates may require alternative approaches, such as a combinatorial formulation containing both immunomodulatory components and conserved influenza antigens.

Further research is necessary to refine approaches to management of influenza, both in prevention and treatment.

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3. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292(11):1333-1340.

Dr Joel F. Aldrich, and  
Dr Richard E. Winn, FCCP,  
NetWork Steering Committee Member



# SLEEP STRATEGIES

## Oral Appliances for the Treatment of Patients With Obstructive Sleep Apnea

*Optimal management requires collaboration with a dentist trained in dental sleep medicine.*

Although the first reported case of oral appliance use was by Pierre Robin in 1934,<sup>1,2</sup> recognition of the effectiveness of these devices in treating sleep-disordered breathing did not gain momentum until the early 1980s. As oral appliances have evolved and dentists have gained expertise in their use, these devices have become an important part of the management of patients with sleep-disordered breathing. At present, oral appliances are recommended as second-line management for patients with obstructive sleep apnea (OSA) who have mild to moderate disease and who prefer an oral appliance or are intolerant of continuous positive airway pressure (CPAP) therapy.<sup>3,4</sup>

The American Academy of Sleep Medicine's practice parameters for oral appliance management of OSA notes that oral appliances are indicated in patients with mild to moderate OSA who prefer the use of an oral appliance to CPAP.

Oral appliances are also recommended for those patients who do not respond to CPAP, who are not appropriate candidates for CPAP, or who fail treatment attempts with CPAP.<sup>4</sup> Oral appliances should be fitted by qualified dentists who are trained and have experience in the care of oral health. These appliances improve sleep-disordered breathing and subjective measures of sleepiness when compared with no treatment or placebo.<sup>5,6</sup> Although CPAP is more effective at improving sleep-disordered breathing than are oral appliances, oral appliances produce significant improvements in measures of sleep-disordered breathing, blood pressure, and quality of life.<sup>5,7</sup> Of note, oral appliances outperformed upper airway surgery in a head-to-head trial.<sup>8</sup>

Oral appliances have been identified by several names, including mandibular repositioning appliances (MRAs), mandibular repositioning devices (MRDs), mandibular advancement splints (MASs), mandibular advancement devices (MADs), and tongue repositioning or tongue retaining devices (TRDs).

These appliances are divided into two categories: those that advance the mandible (MRA, MAS, MRD, and MADs) and those that reposition and retain the tongue in a forward position (TRDs). Since TRDs are not FDA-approved and have not been extensively studied, they will not be discussed further here.

For clarity, the term "mandibular repositioning appliances" will be used in this discussion. MRAs are viewed by the US Food and Drug Administration as class 2 medical devices. MRAs are typically made in two pieces (upper and lower) and then connected. They can be rigid (monobloc) or adjustable (duobloc), with the upper and lower portions attached by a hook or screw assembly or by elastic bands. They are most often made of acrylic resin and well adapted to the teeth for retention purposes.

Adjustable devices are more popular and effective, as they can incrementally advance the lower jaw forward and downward. Many adjustable devices allow for lateral movements of the mandible. This attribute is especially beneficial for patients with OSA who experience bruxism. Devices made of thermoplastic (also known as "boil and bite") are not considered custom-made appliances and do not perform as well.<sup>9</sup>

### How MRAs Work

MRAs work by moving the mandible down and forward, which opens the posterior airspace and pulls the tongue forward. Mandibular protrusion by means of an MRA results in a significant increase in the airway diameter, especially in the oropharyngeal cross-sectional area, in both obese and nonobese subjects.<sup>5,10,11</sup> This increase in airway caliber results in increased airflow, reduced snoring, and improved sleep-disordered breathing.

### Side Effects and Contraindications

Side effects of MRAs include temporomandibular joint and facial pain or discomfort, temporomandibular joint noises, minor tooth movement, changes in occlusion, and skeletal changes, including increased facial height.<sup>5,11,12</sup>

Although oral appliances can be used successfully in patients who grind their teeth, use of an MRA that allows for adequate lateral and anterior-posterior movement may be less likely to exacerbate temporomandibular joint pain.

Most side effects that with MRAs are minor and temporary and do not

significantly affect appliance use.<sup>5,11,12</sup>

Contraindications to the use of MRAs include severe temporomandibular joint pain, insufficient teeth to retain the appliance during usage (eight teeth is probably the minimum), teeth that are compromised by periodontal disease, and a limited mandibular range of motion.<sup>10</sup>

### Oral Appliance Management of the Patient With OSA

Oral appliances are an important part of the armamentarium for OSA management. Optimal management of patients with sleep-disordered breathing requires collaboration between a sleep physician and a dentist who is well trained in dental sleep medicine.

When evaluating a patient with OSA for an oral appliance, the dentist does a dental sleep workup, which includes a thorough review of the medical history, an evaluation of the nasal cavity, and an in-depth evaluation of the oral cavity and the temporomandibular joints and associated structures. Impressions for study and working models are taken, as well as a panoramic radiograph or other imaging.

After an appliance is inserted, the dentist needs to follow up with the patient on a weekly or biweekly basis to assess if the appliance is having an effect. If the appliance is not having an effect, it is then titrated (by moving the mandibular, or lower unit, forward) until it does or it is determined that it is not going to work.

A maximum titration of 75% of the patient's protrusion is generally considered the endpoint for titration. A repeat sleep study is recommended to assess the efficacy of the appliance, once it has been titrated,<sup>4</sup> but it is the author's experience that this happens rarely.

Once efficacy of the appliance is confirmed, continued follow-up by the dentist is essential in order to assess tooth movement and other side effects. The patient is generally seen every 6 months for the first year and at least once a year thereafter.

The ACCP Sleep Medicine NetWork collaborated with the American Academy of Orofacial Pain to produce a printable patient education brochure about oral appliances. This is available on the ACCP Web site at [www.accpstorage.org/newOrganization/patients/oralAppliances.pdf](http://www.accpstorage.org/newOrganization/patients/oralAppliances.pdf).

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DR DAVID D. GUTTERMAN, FCCP

## PRESIDENT'S REPORT Progress and Congratulations

After only a few weeks, an amazing amount of activity has transpired since CHEST 2010! The meeting was very successful with over 4,700 attendees. Kudos to Drs Bob Levy and Ann O'Donnell for a well-run and educationally stimulating conference. I wish to thank the dozens of people who took my offer and introduced themselves during CHEST and talked about how they would like to be more involved with the College. Their enthusiasm was one of the highlights of the meeting for me. In the past several weeks, the ACCP leadership and staff have been studying the many comments and suggestions made during the annual meeting with regard to our ongoing review of NetWorks, approach to advocacy, and the ACCP Governors. We are also finalizing our approach to conflict of interest, with a policy and implementation plan to be distributed soon. The College will define individual and societal guidelines and procedures for appropriate restriction of bias and ensuring compliance across all ACCP activities and functions.

I would like to update you on two promises I made during the Opening Ceremony in Vancouver. Critical to the success of our new strategic plan is enhanced communication that supports bidirectional input. To enhance collaboration between ACCP members and Presidential leaders, the College is launching a new blog on its Web site. From the Presidents will feature

regular blogs from me, as ACCP President; Dr Suhail Raoof, FCCP, ACCP President-Elect; Dr Darcy D. Marciniuk, FCCP, ACCP President-Designate; and Dr Kalpalatha K. Guntupalli, FCCP, ACCP Immediate Past President, about the College, medical and health-care issues, the profession, and other member-related topics of interest. First, we want to directly inform members regarding issues important to the ACCP. Second, we want to encourage two-way conversations by soliciting feedback from members. Importantly, this is a direct link between membership and the President. The more engaged our members, the more informed the leadership will be. More thorough vetting of issues and projects should lead to stronger final products. This is one step in a more comprehensive approach to improved communication that includes a regular Leadership Newsletter and the ACCP News-Brief, which is e-mailed to all members. Our communication efforts set a new standard just last month, when *CHEST* became the first North American respiratory-focused journal to have its own iPhone® and iPad® app. As we modernize our IT systems, look for more innovations to come!

Progress has been made on my goal to create a Presidential Task Force on Diversity and Disparity. I am excited to announce that Dr Marilyn Foreman, MS, FCCP, Department of Medicine, Morehouse School of Medicine in Atlanta, GA, has agreed to chair this task force. Dr Foreman will select task force members and convene an initial meeting at the ACCP offices in January 2011. The work of this task

force is a critical component of the College's effort to remove barriers to effective patient care that are based on cultural, ethnic, and societal status. Marilyn Lederer, CPA, Executive Director of The CHEST Foundation, will oversee staffing of this task force.

I anticipate that the task force will develop a plan with two components. First, the plan will align with the College's strategic plan, allowing us to more consistently tap into the inherent diversity of our membership and staff in conducting our business. Second, the plan should inform our efforts to eliminate disparities in health care through education, legislation, guideline dissemination, and incorporation of best practices in health-care delivery.

Finally, I wish to recognize two major achievements of Dr Suhail Raoof, FCCP, President-Elect of the ACCP. He has been selected as a Master of the American College of Physicians. This honor recognizes his stellar personal character and eminence in the practice of medicine. In addition, Dr Raoof has been nominated for membership in the Fleischner Society, the pre-eminent international society for thoracic radiology. Dr Raoof's wisdom, leadership, and dedication continue to be of exceptional benefit to the ACCP.

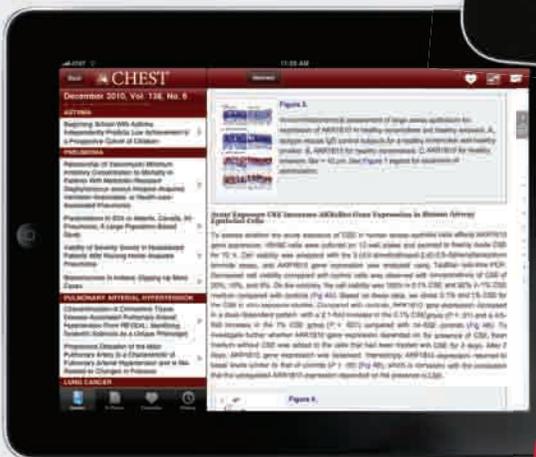
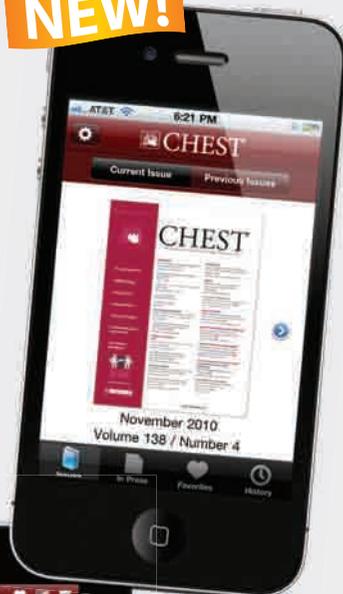
I hope everyone had a safe and enjoyable holiday season, and I extend my best wishes for the new year. Holiday tip: As you shovel snow from your driveway this winter, think about Hawaii and CHEST 2011 to keep warm. It has worked for me already this season!

### CHEST Journal App

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Make The Most Of It

The CHEST Foundation is pleased to introduce its new OneBreath campaign, an exciting public-facing campaign that incorporates its three pillars: education, care, and community. OneBreath: Make The Most Of It emphasizes that living well means breathing well and inspires people to take care of their lungs and heart, never taking their next breath for granted.

The Foundation's mission remains the same: to provide prevention and education programs and valuable resources in cardiopulmonary and critical care medicine. The four focus areas of tobacco prevention and cessation, humanitarian service, clinical research, and critical care/end-of-life care, continue to be the core programming elements.

Support OneBreath and Learn More  
[onebreath.org](http://onebreath.org)

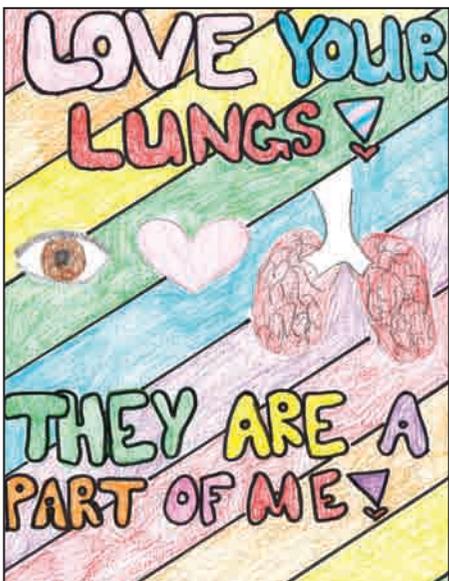
## Poster Contest Spreads Message To Love Your Lungs

“Love Your Lungs” Poster Contest winner Bailey Selecky’s winning design was displayed on T-shirts for participants of the CHEST 2010 5K Walk/Run held on Tuesday, November 2. “Being healthy and breathing strong is very important to me as I am a student athlete and need to be in great physical shape in order to compete and play to

the best of my ability,” says Bailey. She also thanks the Ambassadors Group for letting her help spread the important message to “Love Your Lungs.” Each year, the Ambassadors Group sponsors the poster contest, which is open to all youth, ages 8 to 14. Contact [lfulton@chestnet.org](mailto:lfulton@chestnet.org) for 2011 entry forms or more information. ■



COURTESY BAILEY SELECKY



COURTESY ACCP

The winning poster in the “Love Your Lungs” Poster Contest was created by Bailey Selecky, a student athlete who enjoys “being healthy and breathing strong.”

## Product of the Month

### CHESTSOUNDINGS – CHEST 2010 Symposia Webcasts

The CHESTSOUNDINGS Webcasts provide you with the opportunity to review the clinical information relevant to the chest professional health-care community presented during the Morning Educational Symposia sessions during CHEST 2010.

The Webcast presentations can be conveniently viewed at [www.chestnet.org/accp/chestsoundings](http://www.chestnet.org/accp/chestsoundings).

These resources present various hot-topic medical issues relevant to

your clinical practice and the care you provide to your patients.

We trust this educational medium will prove useful and also serve as a catalyst for you to share your innovative ideas, opinions, and challenges faced within your own medical community.

This resource is fun and collaborative. After you view the activities, you may claim credit via the ACCP continuing medical education site at <https://accp.chestnet.org/loginWA/LoginDispatchAction.do?wa=cme3>. ■

## COPD Alliance Spirometer Giveaway

Registered Respiratory Therapist and asthma educator Diane Rhodes of San Antonio was the winner of the COPD Alliance spirometer giveaway during CHEST 2010.

Members of the newly launched COPD Alliance presented Ms. Rhodes with a new Ndd spirometer as part of the Alliance’s mission to encourage the early

diagnosis of COPD. Ms. Rhodes plans to use the spirometer for screening the employees of the school district

where she works; doing community screenings at clinics in the San Antonio area; and monitoring lung function in more than 200 children with asthma who she counsels. ■



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**CHEST 2010** 

October 30 - November 4  
Vancouver, BC, Canada

  
2010 The Year of the LUNG

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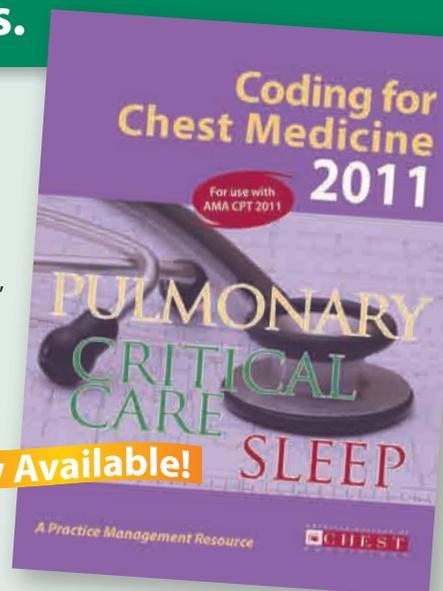
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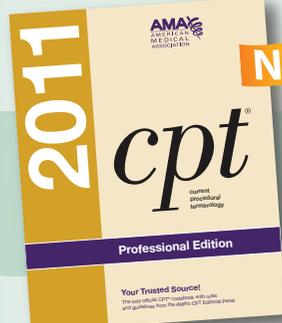
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AMERICAN COLLEGE OF CHEST PHYSICIANS

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

## Volunteers Reach Out to Children During Annual Meeting

*The CHEST Foundation and the ACCP Industry Advisory Council 2010 Community Outreach Event*

On Monday, November 1, during CHEST 2010, more than 40 ACCP and Ambassadors Group member volunteers attended a training session and then boarded a bus to Laura Secord Elementary School in Vancouver. This was the 12th year that volunteers from both the US and international locations reached out to children in the annual CHEST meeting's host city to present about lung health and the dangers of tobacco. Approximately 100 6th graders interacted with the presenters and "student buddies" during this program, which utilizes different aspects of The Foundation's Lung Lessons<sup>SM</sup> program. Comments gathered after the program indicate that the message made it

to the young listeners and included:

"I learned a lot more about how smoking affects your lungs. I will never smoke, so I can stay healthy and live longer."

"I learned that rat poison is in cigarettes."

"All cigarettes are bad, even if they (advertisers) say it's good."

The ACCP Industry Advisory Council presented a \$10,000 grant to Vancouver School District 39, which includes Laura Secord Elementary School. The funds will be used for health education classes and other enrichment activities. ■



Monir Almassi (left) and Dr Norma Braun present tips for good lung health to elementary schoolchildren.

COURTESY ACCP

## Many Winners at CHEST 2010—Congratulations!



### ACCP Honor Awards

- ▶ *Soffer Award for Editorial Excellence*  
Armin Ernst, MD, FCCP
- ▶ *Alton Ochsner Award Relating Smoking and Health*  
Jerome S. Brody, MD  
Kenneth E. Warner, PhD

### Canadian Thoracic Society Awards

- ▶ *CTS Annual Christie Memorial Lecturer*  
Jerome A. Dempsey, PhD
- ▶ *CTS Institute of Circulatory and Respiratory Health Distinguished Lecturer in the Respiratory Sciences*  
James C. Hogg, MD, PhD, FCCP

### The CHEST Foundation Awards

- ▶ *Third GlaxoSmithKline Distinguished Scholar in Respiratory Health*  
Sandra G. Adams, MD, FCCP
- ▶ *D. Robert McCaffree, MD, Master FCCP Humanitarian Awards*  
\$10,000 Humanitarian Award  
Robert C. Hyzy, MD, FCCP
- ▶ *\$7,500 Humanitarian Awards*  
Margaret A. Clark, RRT  
Kevin R. Flaherty, MD, FCCP
- ▶ *Syed S. Naqvi, MD, FCCP*  
C. Sola Olopade, MD, FCCP
- ▶ *\$5,000 Ambassadors Group Humanitarian Recognition Award*  
Lata R. Casturi, MA

- ▶ *American Lung Association and The CHEST Foundation Asthma Clinical Patient Care Research Award*  
Shamsah Kazani, MBBS
- ▶ *Roger C. Bone Advances in End-of-Life Care Award*  
Dee W. Ford, MD, FCCP
- ▶ *Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency*  
Ann E. Tilley, MD
- ▶ *Association of Specialty Professors and The CHEST Foundation of the ACCP Geriatric Development Research Award*  
Jessica Y. Chia, MD
- ▶ *The CHEST Foundation California Chapter Clinical Research/Medical Education Award*  
Hubert Chen, MD, FCCP

- ▶ *The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women's Lung Health*  
Jacob Allan Udell, MD

### Alfred Soffer Research Award Winners

- ▶ *\$1,500 award winners*  
Mary Cataletto, MD, FCCP  
Matthew J. Schuchert, MD
- ▶ *\$1,000 award winners*  
Sneh Arora, PhD  
Christopher Carroll, MD, FCCP  
Lee Morrow, MD, FCCP  
Ran Wang, MD

### Young Investigator Award Winners

- ▶ *\$2,000 award winners*  
Takahiro Nakajima, MD  
Bryon N. Johnson, DO
- ▶ *\$1,250 award winners*  
Laura Barber, MD  
Michelle Kompare, MD  
Ara Chrissian, MD  
Abdelbaset Mohamed Saleh, MD

### Top Five Poster Award Winners

- ▶ William Carroll, MD  
Renee Benson, MD  
Caroline Chapman, PhD  
David S. Hui, MD, FCCP  
Ji-Young Son

### Case Report Award Winners

- ▶ Thomas C. Iden III, MD  
Aditya Gupta, MBBS  
Rupesh K. Dave, MD  
Nishant Gupta, MD  
Jarrod T. Bruce, MD  
Ankur Kalra, MD  
Abhijit A. Raval, MD  
David Wallace, MD  
Heba Ismail, MBChB  
Jamie L. Bessich, MD  
Jorge E. Guerrero Espinosa, MD  
Garrett Bird, MD  
Krithika Ramachandran, MD  
Sonali Bose, MD  
Nichole T. Tanner, MD  
Sunita Mulpuru, MD  
Jessica E. Freyer, MD  
Arvind Ponnambalam, MD  
Leon C. Bass, MD  
Anushya Chelvanathan, MBChB  
Muhammad T. Akbar, MD

- ▶ Luis A. Martin-Del-Campo, MD  
Surya Prakash Bhatt, MD  
Tomio Miyai, MD

### CHEST 2010 Bingo Winners

- ▶ *CHEST Bingo*  
Alesia S. Svymbersky, PA  
Andre L. Smith, MD, FCCP  
Rita Wittmann, MD  
Brent Toney, DO  
Anwar M. Haque, MD
- ▶ *COPD Bingo*  
Maximiliano A. Tamae Kakazu, MD  
Chamani Illamperuma, MBBS  
Leticia Mendoza Muzquiz, MD, FCCP  
Jane Wheeler, MD  
Maria Paz B. Meteó, MD
- ▶ *PAH Bingo*  
Tony Abed, MD, FCCP  
Ericilia Arias, MD, FCCP  
Steven Chambers, MD, FCCP  
Michael Gabilovich, MD, PhD, FCCP  
Nelson Yu, MD

### Best Educational Activity, Clinical Resource Center Clusters

- ▶ *Airway*  
Broncus Technologies, Inc.
- ▶ *Cardiovascular*  
Gilead Sciences, Inc.
- ▶ *Critical Care*  
Symbionix USA Corporation
- ▶ *Diagnostics*  
Morgan Scientific Inc.
- ▶ *Professional Development*  
COPD Alliance
- ▶ *Sleep*  
ResMed

### CHEST Challenge Winners

- ▶ *First Place: National Capital Consortium Pulmonary and Critical Care Fellowship Program*  
CPT Matthew Aboudara  
LT Gregory Fuhrer, MC, USN  
LT Scott Parrish, MC, USN
- ▶ *Second Place: Maimonides Medical Center*  
Prashant Gundre, MBBS  
Arjun Madhavan, MBBS  
Kavan Ramachandran, MBBS
- ▶ *Third Place: Baylor College of Medicine*  
Soma Jyothula, MBBS  
Amarbir Mattewal, MD  
Vishal Sawhney, MD

CHEST 2011

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Coming January

## CHEST 2011 Opportunities

### Call for Abstracts

Submit an abstract of your original investigative work for presentation at the meeting. Submission is free to ACCP members.

Watch for details and submission opportunities, coming January 31.

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

Submission deadline: May 4

### Call for Case Reports

ACCP affiliate members are invited to submit case reports for presentation during special sessions.

Watch for details and submission opportunities, coming January 31.

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

Submission deadline: May 4

### The CHEST Foundation 2011 Awards Program

More Than \$500,000 To Be Awarded

The CHEST Foundation tradition of recognizing and rewarding health-care professionals for volunteer service, leadership, and clinical research continues in 2011. You could be eligible.

Watch for details and application opportunities, coming in January.

[onebreath.org](http://onebreath.org)

Application deadline: May 4

AMERICAN COLLEGE OF  
CHEST  
PHYSICIAN



# Humanitarian Award Winners, Outgoing Chair Honored

The CHEST Foundation's 12th Annual Making a Difference Awards Ceremony and Presentation during CHEST 2010 focused on the D. Robert McCaffree, MD, Master FCCP Humanitarian Award winners. This year's award winners and their projects were:

- ▶ Margaret A. Clark, RRT, Not One More Life Asthma Clinic, Atlanta, GA
- ▶ Dr Kevin R. Flaherty, FCCP, Faith Medical Clinic, Pinckney, MI
- ▶ Dr Robert C. Hyzy, FCCP,

Toward a Sustainable Model of Care Delivery to the Indigent of Belen, Peru

▶ Dr Syed S. Naqvi, FCCP, Sustainable Health-care Initiatives Now Empowering (SHINE), USA in Affiliation with Comprehensive Disaster Response Services (CDRS) in Chikar, District Muzaffarabad, Pakistan

▶ Dr C. Sola Olopade, FCCP, Protecting Women and Children From Exposure to Indoor Air Pollution From Burning Biomass in Eruwa, Abanla, and Igbo Ora, Nigeria

The Ambassadors Group Humanitarian Award winner was Lata R. Casturi, MA, Project S.I.E.S.T.A. (Students Involved in the Education About Sleep Hygiene for Teen Adolescents), Houston, TX.

Each award winner prepared a video clip of their project, and these will be posted on The Foundation's YouTube channel very soon. We encourage you to take the time to view them ([www.youtube.com/user/ChestFoundation](http://www.youtube.com/user/ChestFoundation)).

The CHEST Foundation was proud to have the following corporate partners sponsor this year's dinner: AstraZeneca LP; Boehringer Ingelheim Pharmaceuticals, Inc.; Eisai, Inc.; Genentech and Novartis; Gilead Sciences, Inc.; Merck & Co., Inc.; Ortho-McNeil Janssen Pharmaceuticals; Pfizer, Inc.; and sanofi-aventis, US.

Another highlight of the evening was a tribute to outgoing Chair of The CHEST Foundation Board of Trustees, Dr Robert G. Johnson, FCCP. A tribute video was shown depicting



Honoree Dr Robert G. Johnson, FCCP (left), outgoing Chair of The CHEST Foundation Board, with Dr John C. Alexander Jr, FCCP.

Dr Johnson's long career as ACCP's Past President (2000) and the many accomplishments during his tenure on The Foundation's Board (2000-2010). Close friends and colleagues took the opportunity to participate in this farewell tribute by sharing some of their own humorous stories.

Dr Johnson's contributions to The CHEST Foundation include the formation of a Development Committee

responsible for the oversight of fundraising and establishing endowments, as well as the reorganization of the Awards Committee to become a repository for all College awards. The Foundation is pleased that Dr Johnson has accepted the role of Chair of the OneBreath™: Make The Most Of It initiative and will remain a resource to The CHEST Foundation as it launches this important initiative.



Humanitarian award winners (L-R): Margaret A. Clark, RRT; Dr Kevin R. Flaherty, FCCP; Dr Robert C. Hyzy, FCCP; Dr Syed S. Naqvi, FCCP; and Dr C. Sola Olopade, FCCP.

## Glimpses of CHEST 2010 in Vancouver



CHEST Challenge winners from the National Capital Consortium Pul/CC Fellowship Program.



Dr Alfred Soffer, Master FCCP, takes a turn at virtual reality learning in Experience ACCP.



Meeting attendees appreciated the chance to learn new procedures through simulation.



There was plenty of activity at Experience ACCP in the exhibit hall.



The Cyber Café gets more popular among meeting attendees with every passing year.

Pictures from CHEST 2010 are available for viewing and purchase at [www.lagniappstudio.com/chest2010](http://www.lagniappstudio.com/chest2010). Plan now to attend CHEST 2011, Oct. 22-27, in Honolulu, Hawaii.

# Home Testing for Sleep Apnea Not Inferior

BY SUSAN LONDON  
Elsevier Global Medical News

VANCOUVER, B.C. – Recent research on the use of home testing for the diagnosis of obstructive sleep apnea and initiation of therapy suggests that “home testing is here to stay,” Dr. Charles W. Atwood Jr., FCCP, said at CHEST 2010, the annual meeting of the American College of Chest Physicians.

For more than 30 years, physicians have relied on the traditional polysomnography performed in the sleep laboratory to diagnose sleep apnea, according to Dr. Atwood. But with growing awareness of the condition and its prevalence, the number of people needing testing could overwhelm capacity.

“If you take the millions and millions and millions of people in the United States alone who have sleep apnea and try to feed them through the relatively small funnel of traditional sleep labs, then you are going to have big bottlenecks,” he said, adding that such bottlenecks already exist in some areas.

However, home-testing devices must meet certain key requirements before they are ready for widespread use. For example,

they have to be simpler than those used in the lab. “Perhaps we can get by with fewer [physiological] signals, but we need to understand what the key signals are,” commented Dr. Atwood, a pulmonologist and sleep medicine specialist with the VA Pittsburgh Healthcare System and the University of Pittsburgh Medical Center.

Home testing devices will also need to be accurate, with high sensitivity and specificity, and “there is no single device I would say today that is perfect in both these regards,” he noted. Finally, they must be easy to use and durable, given the demands of in-home use.

Roughly 95 studies conducted between 1990 and 2006 evaluated home testing (also called portable monitoring) for the diagnosis of obstructive sleep apnea. Collectively, they had some limitations, such as their single-site nature, small and usually homogeneous populations, and varying degrees of rigor in design.

“And they frequently focused on the highest-risk subjects: These were middle-aged men who were overweight, snored, and were sleepy, so [they were] the very low-hanging fruit for typical sleep apnea,” Dr. Atwood said.

These studies showed some mixed re-

sults when it came to the diagnostic performance of home testing relative to lab testing. “There is no perfect study, at least so far, in this area, but some have come pretty close,” he commented.

Three more-recent studies suggest that home testing is at least not inferior to lab testing for sleep apnea diagnosis and initiation of continuous positive airway pressure (CPAP) therapy, according to Dr. Atwood.

In the first study, conducted in 68 people with a high likelihood of sleep apnea, the apnea-hypopnea index on CPAP and Sleep Apnea Quality of Life Index scores at 3 months did not differ significantly between a sleep lab and an ambulatory approach (Ann. Intern. Med. 2007;146:157-66). The rate of adherence to CPAP was better with the latter.

In the second study, which involved 102 patients with sleep apnea symptoms and no major comorbidities, all of a variety of sleep and quality of life outcomes after 4 weeks of CPAP were similar with a standard lab diagnosis and treatment approach vs. a home approach (Chest 2010;138:257-63).

The third study, the Veterans Sleep Apnea Treatment Trial (VSATT), is the largest study of home testing in North America to date, according to Dr. Atwood, one of the principal investigators.

“The VA is ill equipped to manage sleep apnea in a conventional way because we have relatively few numbers of traditional sleep labs,” he noted.

“Our study differed from basically all of the other studies in the literature in that we had very broad inclusion criteria and very nonrestrictive exclusion criteria,” Dr. Atwood noted. For example, patients with comorbidities could participate as long as their condition was stable.

Patients were randomized to lab testing or home testing, followed by initiation of CPAP for those with positive results.

Among the 223 who were started on CPAP, the home and lab groups had

similar demographics. The average apnea-hypopnea index was 41 for the former and 45 for the latter. The Functional Outcomes of Sleep Questionnaire (FOSQ) total score was about 15 in each group.

Results showed that the mean adjusted improvement in FOSQ total score between baseline and 3 months was identical in the two groups, at 1.79 points. And within each group, patients had significant improvements in the total score as well as its individual components.

Both home and lab groups also had significant improvements on the Epworth Sleepiness Scale (–2.6 and –2.9, respectively), the mental health component of the 12-item Short Form Health Survey (+2.5 and +3.0), and the Center for Epidemiologic Studies–Depression scale (–1.4 and –2.2). Neither group improved significantly on the psychovigilance task or the physical health component of the 12-item Short Form Health Survey.

When it came to adherence, which was monitored with smart cards, the mean adjusted number of CPAP hours daily was 3.42 in the home group and 2.99 in the lab group, a difference that was not significant. Cost-effectiveness analyses are still ongoing.

“We concluded that the functional improvement with CPAP for sleep apnea is not worse when treated in the home setting vs. the sleep lab,” Dr. Atwood said. “We believe ... home-based sleep apnea diagnosis and initiation of CPAP therapy is an effective way to treat sleep apnea.”

While home testing won’t entirely replace laboratory polysomnography, Dr. Atwood suggested trying to “integrate home sleep testing with full polysomnography in a clinically rational way.”

Dr. Atwood reported that he received research support from Embla, Resmed, and Respiroics, and is a consultant to Embla and Itamar Medical, all of which manufacture testing and treatment devices for sleep disorders. ■



**‘Functional improvement with CPAP for sleep apnea is not worse when treated in the home setting vs. the sleep lab.’**

DR. ATWOOD

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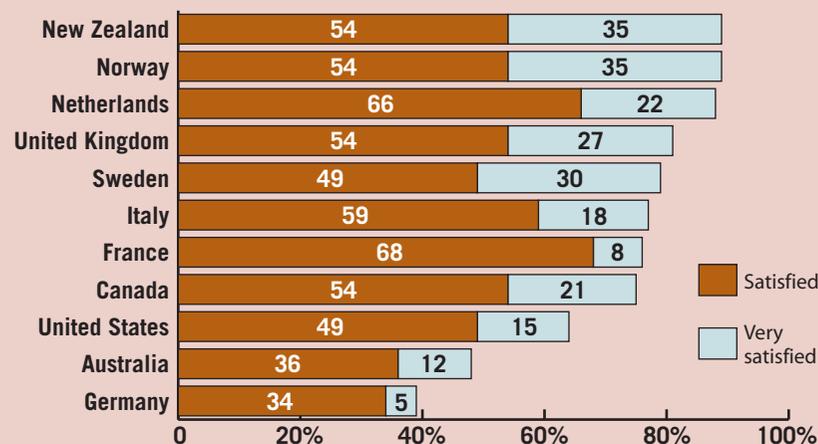
The VA Medical Center in Milwaukee, Wisconsin is a large tertiary care facility affiliated with the Medical College of Wisconsin. Openings exist for pulmonary and critical care medicine physicians to join the section of Pulmonary, Critical Care Medicine and Sleep Medicine. Qualified candidates must be Board certified or eligible in Pulmonary Disease and Critical Care Medicine and have the qualifications for a Faculty appointment at the Medical College of Wisconsin. Fellowship training in sleep medicine is a plus. Professional and academic opportunities exist through the Medical College of Wisconsin and the Department of Veterans Affairs. Interested candidates should send a current Curriculum Vitae, referencing Pulmonary, to: Clement J. Zablocki VA Medical Center, Human Resources Attn: Prudy Kitterman, 5000 W. National Avenue, Milwaukee, WI 53295, prudy.kittermann@va.gov fax to 414-382-5296. Additional inquiries should be directed to Andreea Antonescu, MD at 414-384-2000 X42765 or email to andreea.antonescu-turcu@va.gov

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## DATA WATCH

### Satisfaction With Medicine Low Among U.S. Physicians



Note: Data collected from 10,320 primary care physicians from February to July 2009. Source: The Commonwealth Fund

# CPAP Reverses Left Atrial, Ventricular Remodeling

BY BRUCE JANCIN  
Elsevier Global Medical News

SAN ANTONIO – Six months of continuous positive airway pressure therapy markedly improved adverse left ventricular and atrial remodeling in patients with moderate to severe obstructive sleep apnea in a prospective study.

Diastolic as well as systolic abnormalities were reversed, raising the welcome prospect that CPAP is likely to prevent the development of one of the most dreaded complications of severe obstructive sleep apnea (OSA) – chronic heart failure – although this point remains speculative, Dr. Saleh Al-Mutairi said at the annual meeting of the Associated Professional Sleep Societies.

He recruited 32 patients with newly diagnosed moderate to severe OSA for the study, which involved serial follow-up by cardiac magnetic resonance (CMR), echocardiography, and cardiac biomarkers through 6 months of individually titrated CPAP therapy.

The subjects averaged 51 years of age, with a mean baseline apnea-hypopnea index of 53 events/hr and a body mass index of 34.5 kg/m<sup>2</sup>. None of the participants had known cardiac disease. Adherence to CPAP was good. The patients' weight didn't change significantly during the study, and those being treated for hypertension remained on the same doses of medication throughout the follow-up period.

Other studies have shown improvement in left ventricular dysfunction with CPAP, but they were short-term trials. This is the first study with follow-up as long as 6 months using both CMR and echocardiography, said Dr. Al-Mutairi of the University of Manitoba, Winnipeg.

He focused on the CMR results because he considers that technology more reliable than echocardiography for assessing ventricular size and function. The echo findings, however, corroborated the CMR results.

Most of the left ventricular measurements followed during the study were abnormal at baseline. The 6-month results included a 25% reduction from baseline in left ventricular end-diastolic volume and a 19% decrease in left ventricular mass. (See box, above right.)

Dr. Al-Mutairi drew particular attention to the 30% reduction in left atrial volume index, which he considers highly encouraging. "The treatment of OSA with CPAP may prevent the left atrial remodeling measured by CMR and echo as the left atrial volume index. This is a very important point, given the association between the left atrial volume and cardiovascular events," he observed.

There was no significant change in C-reactive protein, brain natriuretic peptide, or other cardiac biomarkers during the 6 months of CPAP use.

The mechanism by which OSA is thought to predispose to heart failure involves an exaggerated negative thoracic

pressure in response to the apneic episodes. This presumably leads to increased left ventricular systolic transmural pressure, which the left atrium resists, with resultant increased compliance and atrial overstretching, Dr. Al-Mutairi explained.

Dr. Al-Mutairi reported having no financial conflicts.

## Key Cardiac Magnetic Resonance Changes Within 6 Months of CPAP

	Baseline	Follow-up
Left ventricular end-systolic volume	68 mL	53 mL
Left ventricular end-diastolic volume	199 mL	150 mL
Left ventricular mass	184 g	149 g
Left atrial volume index	49 mL/m <sup>2</sup>	34 mL/m <sup>2</sup>

Notes: Based on a study of 32 patients with moderate to severe obstructive sleep apnea. All reductions are statistically significant.  
Source: Dr. Al-Mutairi

### TYGACIL® (tigecycline) Brief Summary

See package insert for full Prescribing Information. For further product information and current package insert, please visit [www.pfizer.com](http://www.pfizer.com) or call our medical communications department toll-free at 1-800-934-5556.

#### INDICATIONS AND USAGE

TYGACIL is indicated for the treatment of adults with complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* gr. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*.

TYGACIL is indicated for the treatment of adults with complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* gr. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

TYGACIL is indicated for the treatment of adults with community-acquired pneumonia infections caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*.

#### CONTRAINDICATIONS

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

#### WARNINGS AND PRECAUTIONS

##### Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

##### Hepatic Effects

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

##### Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia

A study of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this study, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator.

##### Use During Pregnancy

TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [see **USE IN SPECIFIC POPULATIONS**].

##### Tooth Development

The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

##### Clostridium difficile-Associated Diarrhea

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, 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 over two 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.

##### Patients With Intestinal Perforation

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

##### Tetracycline-Class Effects

TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.

##### Superinfection

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

##### Development of Drug-Resistant Bacteria

Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

##### ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators <sup>a</sup> (N=2307)
<b>Body as a Whole</b>		
Abdominal pain	6	4
Abscess	3	3
Asthenia	3	2
Headache	6	7
Infection	8	5
<b>Cardiovascular System</b>		
Phlebitis	3	4
<b>Digestive System</b>		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
<b>Hemic and Lymphatic System</b>		
Anemia	4	5
<b>Metabolic and Nutritional</b>		
Alkaline Phosphatase Increased	4	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	3
Healing Abnormal	4	1
Hypoproteinemia	5	3
SGOT Increased <sup>b</sup>	4	5
SGPT Increased <sup>b</sup>	5	5
<b>Nervous System</b>		
Dizziness	3	3
<b>Skin and Appendages</b>		
Rash	3	4

<sup>a</sup> Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.

<sup>b</sup> LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In all Phase 3 and 4 studies that included a comparator, death occurred in 3.9% (147/3788) of patients receiving TYGACIL and 2.9% (105/3646) of patients receiving comparator drugs. An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL treated patients versus comparator. The cause of this increase has not been established. This increase should be considered when selecting among treatment options. (See Table 2.)

Table 2. Patients with Adverse Events with Outcome of Death by Infection Type

Infection Type	n/N	TYGACIL %	Comparator n/N	Comparator %	Risk Difference* % (95% CI)
<b>Approved Indications</b>					
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.5, 1.9)
cIAI	40/1382	2.9	27/1393	1.9	1.0 (-0.3, 2.2)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.3, 2.7)
Combined	64/2640	2.4	44/2628	1.7	0.7 (-0.0, 1.6)
<b>Unapproved Indications</b>					
HAP	65/467	13.9	56/467	12.0	1.9 (-2.6, 6.4)
Non-VAP <sup>a</sup>	40/336	11.9	42/345	12.2	-0.3 (-5.4, 4.9)
VAP <sup>a</sup>	25/131	19.1	14/122	11.5	7.6 (-2.0, 16.9)
RP	11/128	8.6	2/43	4.7	3.9 (-9.1, 11.6)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.8, 2.2)
Combined	84/1148	7.2	61/1018	6.0	1.2 (-1.0, 3.4)

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

\* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups.

<sup>a</sup> These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see **WARNINGS AND PRECAUTIONS**].

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CAP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%).

For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies: Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia, hyponatremia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

##### Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Anaphylaxis/anaphylactoid reactions, acute pancreatitis, hepatic cholestasis, and jaundice.

##### DRUG INTERACTIONS

###### Warfarin

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

###### Oral Contraceptives

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

##### USE IN SPECIFIC POPULATIONS

###### Pregnancy

Teratogenic Effects—Pregnancy Category D [see **WARNINGS AND PRECAUTIONS**]

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, <sup>14</sup>C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bone structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg-hr/mL and 6 mcg-hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

###### Nursing Mothers

Results from animal studies using <sup>14</sup>C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman [see **WARNINGS AND PRECAUTIONS**].

###### Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years has not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended [see **WARNINGS AND PRECAUTIONS**].

###### Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 286 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

###### Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see **CLINICAL PHARMACOLOGY (12.3)** and **DOSAGE AND ADMINISTRATION (2.2)** in full Prescribing Information].

###### OVERDOSAGE

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD<sub>50</sub>) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD<sub>50</sub> was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

This Brief Summary is based on TYGACIL direction circular W10521C013 ET01, revised 09/09.



TYGACIL is in the 2009 IDSA/SIS guidelines for cIAI and the 2009 SIS guidelines for cSSSI.<sup>1,2</sup>

## Expanded broad-spectrum coverage<sup>3\*</sup> is on your side

Gram positives  
Gram negatives  
Atypical  
Anaerobes

\*TYGACIL does not cover *Pseudomonas aeruginosa*.

### TYGACIL is indicated for the treatment of adults with:

- **Complicated skin and skin structure infections** caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*
- **Complicated intra-abdominal infections** caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*
- **Community-acquired bacterial pneumonia** caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*

### Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options**
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.** TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary of Prescribing Information on adjacent page.

**References:** 1. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:133-164. 2. May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect.* 2009;10:467-499. 3. TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.

**Tygacil**  
tigecycline IV

Expanded broad-spectrum coverage

