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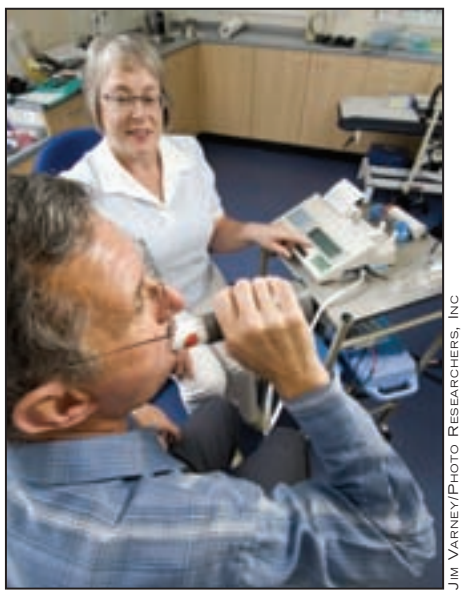

JIM VARNEY/PHOTO RESEARCHERS, INC

The investigators tested for an association between single-nucleotide polymorphisms in the *MMP12* gene and lung function as assessed by FEV_1 in cohorts participating in seven clinical trials.

Gene Linked to Lung Protection in Asthma

BY MARY ANN MOON
Elsevier Global Medical News

A variation in the *MMP12* gene appears to be associated with beneficial pulmonary effects in children who have asthma and in adults who smoke, particularly in smokers with COPD, according to a study published online in the New England Journal of Medicine.

"Our results suggest that variants of *MMP12* are determinants of the level of lung function in subjects who are at risk for airflow obstruction," said Dr. Gary M. Hunninghake and Dr. Michael H. Cho of Brigham and Women's Hospital, Boston, and their research associates.

The investigators tested for an association between single-nucleotide polymorphisms (SNPs) in the *MMP12* gene and lung function as assessed by forced expiratory volume in 1 second (FEV_1) in cohorts participating in seven clinical trials.

The *MMP12* gene encodes matrix metalloproteinase 12, which is produced by macrophages, "the predominant cell type that patrols the lower airspaces under normal conditions and the main inflammatory cell type that is recruited with smoking," the investigators noted.

Matrix metalloproteinases degrade extracellular matrix molecules such as collagen and elastin and are also involved in epithelial repair and the regulation of cytokine and chemokine activity.

The researchers first found that the minor allele of SNP rs2276109 in the *MMP12* gene was significantly associated with increased FEV_1 in children with asthma (but not nonasthmatic children) who were subjects in the Genetics of Asthma in Costa Rica Study.

They then found the same link between the SNP and increased FEV_1 among children taking budesonide—but not among those who were not taking budesonide—in the

See **Asthma** • *page 2*

Officials Caution Against Declaring End to Pandemic

'Up and down' pattern, WHO says.

BY JONATHAN GARDNER
Elsevier Global Medical News

Although the number of infections with the pandemic virus influenza A(H1N1) is plateauing or shrinking in many countries, the World Health Organization has not begun formal discussions about when to declare an end to the pandemic, an agency official said last month.

At a media briefing, Dr. Keiji Fukuda, WHO special adviser on pandemic influenza, said the virus has been following an "up and down" pattern, with some countries already seeing caseloads diminish while others are experiencing increases.

In addition, because the virus could undergo genetic drift that will make it more or less virulent, it is hard to predict whether there will be additional waves in subsequent influenza seasons in both hemispheres, Dr. Fukuda said. As a result, the WHO does not anticipate soon declaring that H1N1 is a seasonal virus subject to annual preparations by public health officials.

"There's no set date for when discussions on a transition would begin," Dr. Fukuda said. "I anticipate that at least at some time in 2010 we'll be discussing this in a more formal way."

British officials echoed Dr. Fukuda's caution. In a press conference on the pandemic, Dr. David Salisbury, director of immunization at the English Department of Health, said, "Everybody is being very cautious about 2010 because we have no idea what will be the seasonal flu and what will happen with this

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INSIDE

Volume-Doubling Time May Reveal Risk

BY MARY ANN MOON
Elsevier Global Medical News

Among people at high risk for lung cancer, volume CT can be used to evaluate noncalcified pulmonary nodules to accurately identify lesions that have a low potential for malignancy, according to a report in the Dec. 3 issue of the New England Journal of Medicine.

Volume CT often detects suspicious nodules in patients who are screened because of their high risk for lung cancer, and "clinicians often face the problem of deciding on the best course of action" in these cases, according to Dr. Rob J. van Klaveren of Erasmus Medical Center, Rotterdam, the Netherlands, and his associates.

"The current practice is to refer … for additional diagnostic evaluation if they have a noncalcified nodule that is larger than 5 mm in diameter," but this often leads to expensive and invasive procedures for lesions that prove to be benign, the investigators noted.

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Pandemic Flu's Future Unclear

Pandemic • *from page 1*

virus when it transitions from its current very powerful state to a seasonal state at a time when the population immunity is expanding, forcing the virus to drift."

Dr. Fukuda said the WHO does not expect to publish a case fatality rate for another 1 to 2 years, as it will take that long for the necessary vital statistics to have been collected to make such an estimate.

In other news, as of mid-December, approximately 60 million people in the United States, about 40% of them children, have received the 2009 pandemic H1N1 influenza vaccine thus far.

Two telephone surveys—one by the Centers for Disease Control and Prevention, Atlanta, the other by the Harvard School of Public Health, Boston—were conducted Dec. 6-12 and 16-17, respectively. The survey findings suggest that about one-half of Americans would like to receive the vaccine, but only about one-third have been able to do so. Many of the initial doses went to targeted high-risk populations; more doses will be available to the general population in the coming days and weeks, the CDC's Dr. Anne Schuchat said Dec. 22 in a telebriefing.

"The H1N1 vaccine supply is getting better and better. Vaccine is becoming available in more and more places and at more and more times," said Dr. Schuchat, director of the CDC's National Center for Immunization and Respiratory Diseases.

The CDC collected survey data for 1,368 adults and 3,243 children. As of the second week of December, those data were extrapolated to estimate that approximately 46 million people had received the vaccine. About 40% were children, a targeted high-risk group.

The more-recent Harvard phone survey involved about 1,600 respondents, including 400 parents. From those data, the CDC increased the estimate of vaccine recipients to about 56 million. Now, nearly a week later, the agency estimates that approximately 60 million have received the vaccine, Dr. Schuchat said.

Dr. Schuchat reiterated that, in order to be fully protected, children who are less than 10 years of age and got one dose of H1N1 vaccine need to receive a second dose 4-6 weeks after the first dose. "It's really important to finish the series," she said.

—Miriam Tucker contributed to this report.

Dr. Mark Metersky, FCCP, comments: *The 1918-1919 influenza pandemic had three waves, so concern regarding a second peak of infections is not merely a theoretical concern.*

Genetic Variant May Protect

Asthma • *from page 1*

Childhood Asthma Management Program. The same link between the SNP and increased FEV_1 existed among children with asthma (but not nonasthmatic children) in the BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiological Survey) study.

Dr. Hunninghake and his colleagues then tested for the same association in adults who were subjects in the Boston Early-Onset COPD Study, the Lovelace Smokers Cohort, and the Normative Aging Study.

The researchers found that the same SNP variation was associated with improved lung function in adults who were current or former smokers, but not in nonsmokers.

Finally, the investigators found that the same *MMP12* variant appeared to protect patients at risk for COPD against the disease in those same three adult cohorts. The absence of the SNP rs2276109 was associated with a 54% increase in the risk of the onset of COPD and a population attributable risk of COPD of 28%.

The findings support the so-called "Dutch hypothesis," which states that asthma and COPD are different manifestations of a single disease entity and suggests that as-yet unknown genetic variants may underlie both asthma and COPD, the investigators said (N. Engl. J. Med. 2009;361[doi:10.1056/NEJMoa0904006]).

Most previous studies of genetic associations in pulmonary function have relied on a single cohort, the study's authors noted.

"A strength of our study is that it included the analysis of multiple measurements of pulmonary function in a large number of subjects—more than 20,000 FEV_1 measurements in more than 8,300 subjects," they added.

THE FINDINGS SUPPORT THE SO-CALLED 'DUTCH HYPOTHESIS,' WHICH STATES THAT ASTHMA AND COPD ARE DIFFERENT MANIFESTATIONS OF A SINGLE DISEASE ENTITY.

"Evidence is accumulating that asthma and COPD share common pathogenetic pathways," noted Dr. Guy G. Brusselle of Ghent (Belgium) University Hospital, in an accompanying editorial. "This study … adds to the accumulating evidence that several mechanisms may lead to the development of COPD" (N. Engl. J. Med. 2009;361[doi:10.1056/NEJMe0919626]).

The new study has several strengths, Dr. Brusselle noted. Those strengths include the inclusion of seven cohorts with more than 8,300 subjects; the replication of an association between the SNP and FEV_1 both in adult smokers and children with asthma; and the researchers' ability to repeat the analyses after stratification for asthma status and smoking status.

"Hunninghake and colleagues have revitalized the Dutch hypothesis and set the scene for future genetic studies of chronic obstructive airway disease," Dr. Brusselle concluded.

Dr. Hunninghake and Dr. Cho reported no conflicts of interest relevant to the study.

Their associates reported receiving support from AstraZeneca Pharmaceuticals, Merck & Co., Johnson & Johnson, Golden Helix Inc., Novartis, GlaxoSmithKline, Sandvik, Sepracor Inc., Genentech Inc., and Phadia AB. ■

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CHEST PHYSICIAN

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FDA Panel Supports Inhaled Antibiotic For Pseudomonas Lung Infection in CF

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

GAITHERSBURG, MD. — Studies of an inhaled formulation of the monobactam antibiotic aztreonam in patients with cystic fibrosis show that it is a safe and effective treatment for *Pseudomonas aeruginosa* lung infections in this population, most of a federal advisory panel agreed.

The Food and Drug Administration's Anti-Infective Drugs Advisory Committee voted 15-2 that the manufacturer, Gilead Sciences Inc., had provided substantial evidence that inhaled aztreonam, administered at a dose of 75 mg three times a day for 28 days, was safe and effective for the proposed indication: the improvement of respiratory symptoms and pulmonary function in patients who have cystic fibrosis (CF) with *P. aeruginosa*. If aztreonam lysine for inhalation (AZLI) is approved, the company plans to market it as Cayston, with a novel, portable handheld nebulizer that delivers the 75-mg dose in 2-3 minutes. The panel was not asked to specifically vote on whether to recommend approval.

Inhaled aztreonam has already been approved for this indication in the European Union, Canada, and other countries. The intravenous formulation was approved in 1986 in the United States for indications that include *P. aeruginosa* infections, but not specifically for CF patients.

Although the FDA raised issues about whether 75 mg three times a day was the best dose, the panel unanimously agreed in a 17-0 vote that this dose had been shown to be safe and effective, although several panelists said that other doses should be studied.

AZLI was compared with placebo in two pivotal placebo-controlled phase III studies of patients aged 6 years and older with CF (mean age was in the mid-20s to early-30s), who had P. aeruginosa and forced expiratory volume in 1 second (FEV1) of 25%-75% (predicted).

In one study, approximately 200 patients received 75 mg of AZLI or placebo twice or three times a day, for 28 days, after completing 28 days of treatment with tobramycin inhalation solution (TOBI), the only FDA-approved inhaled antibiotic approved for treating *P. aeruginosa* in CF patients (approved in 1997). The primary end point—the time that elapsed from the point at which patients started AZLI or placebo to the point at which they needed inhaled or IV anti-pseudomonalantibiotics—was a median of 92 days among those on AZLI, compared with a median of 71 days among those on placebo, a significant difference. Those on AZLI also had improvements in FEV_1, a secondary end point; these improvements were significantly greater than they were in those on placebo.

In a second study, which enrolled 164 patients treated with AZLI or placebo three times a day for 28 days, the primary end point was the change from day 0 to 28 in clinical symptoms, as assessed by the respiratory scores of a CF symptom questionnaire. In both studies, AZLI-treated patients also had significantly better mean changes in FEV_1 over 28 days, a secondary end point, when compared with those on placebo.

The FDA usually follows the recommendations of its advisory panels, which are not binding. ■

Autopsies Reveal That H1N1 Infection Damages Entire Airway

BY ROBERT FINN
Elsevier Global Medical News

The 2009 pandemic influenza A(H1N1) virus damages the entire airway, from the trachea to the alveoli of the lungs, according to the results of 34 autopsies.

All of the autopsies showed evidence of focal or extensive tracheitis and bronchitis, wrote Dr. James R. Gill of the New York City Office of Chief Medical Examiner and his colleagues in a paper published online in the journal Archives of Pathology & Laboratory Medicine. The article will appear in the February 2010 print issue (Arch. Pathol. Lab. Med. 2010;134:e1-9).

In 18 of the 34 cases, investigators observed focal mild to moderate bronchiolitis. In 25 cases, investigators observed focal to extensive diffuse alveolar damage from influenza viral pneumonia. Investigators found evidence of acute bacterial pneumonia in 18 patients; 16 of those patients had streptococci, and 2 patients had staphylococci. Eight of the autopsies revealed acute pulmonary hemorrhage.

"These pathologic findings are strikingly similar to those of published autopsy studies from the 1918 and 1957 pandemics and to a more limited extent from publications investigating seasonal influenza," the investigators wrote.

Victims of seasonal influenza tend to have much less evidence of viral replication in the lung than do victims of the influenza pandemics, including the pandemic resulting from this year's H1N1 virus, said coauthor Dr. Jeffery K. Taubenberger of the National Institute of Allergy and Infectious Diseases (NIAID) in an interview.

Autopsies from victims of the pandemics show much more evidence of serious viral pneumonia, he added, whereas victims of seasonal influenza are more likely to have bacterial pneumonia.

'THESE PATHOLOGIC FINDINGS ARE STRIKINGLY SIMILAR TO THOSE OF PUBLISHED AUTOPSY STUDIES FROM THE 1918 AND 1957 PANDEMICS.'

Investigators obtained CT scans from four of the victims. All four showed a distinctive abnormality called ground-glass opacity. "Our findings suggest that CT can be a valuable tool in identifying patients who will require intensive medical support and to elucidate the pathogenesis of severe disease," the investigators wrote.

The patients involved in the study ranged in age from 2 months to 72 years (median, 41.5 years), and they died between May 15 and July 9, 2009. All had confirmed infections with pandemic H1N1 influenza virus.

Except for two healthy infants aged 2 months and 4 months, all the patients had one or more medical conditions that may have predisposed them to serious complications from H1N1 influenza. The most common comorbidities were obesity, heart disease, and underlying pulmonary disease.

The National Institutes of Health supported the study in part through NIAID. Some of the investigators were NIAID employees. The investigators stated that they had no financial conflicts related to the study. ■

Dr. Nicola A. Hanania, FCCP, comments: *Initial reports suggested that clinical presentation of 2009 influenza A(H1N1) may be similar to seasonal influenza. While this may indeed be the case in a majority of cases, many recent reports have documented that a subgroup of affected patients suffers from severe hypoxemic respiratory failure requiring prolonged mechanical ventilation, occasionally leading to death. This report suggests that multiple sites in the lung are affected in these patients, including the small airways, in addition to the lung parenchyma. These findings suggest that the pulmonary complications in patients suffering from H1N1 influenza may be more extensive than those seen with seasonal influenza. Whether this is related to the higher virulence of the H1N1 virus or to certain underlying host factors needs to be explored further.*

Epitopes Similar in Flu Viruses

BY DENISE NAPOLI
Elsevier Global Medical News

Many of the epitopes present in recently circulating seasonal influenza virus also can be found in the swine-origin pandemic H1N1 influenza virus, raising the possibility that "some level of immunity against [pandemic flu] might exist in the general population."

Indeed, the finding is borne out by reports detailing the incidence of clinically severe pandemic flu, which "so far appears to be similar to that experienced for seasonal flu," according to a study released online Nov. 16 in the Proceedings of the National Academy of Sciences (doi: 10.1073/pnas.0911580106).

An epitope is the site on the surface of an antigen that elicits an immune response.

The authors of the current study, led by Dr. Jason A. Greenbaum of the La Jolla (Calif.) Institute for Allergy and Immunology, looked at epitope databases for seasonal flu, as well as the National Center for Biotechnology Information database and the Global Initiative on Sharing Avian Influenza Data database, which both contain information about swine-origin pandemic flu epitopes.

"A total of 26 B-cell epitopes were found in recently circulating [seasonal] H1N1 strains, whereas 139 CD4 and 78 CD8 T-cell epitopes were found," wrote Dr. Greenbaum and colleagues. Of those, 8 B-cell epitopes were "conserved," or shared by the swine-origin pandemic H1N1 strain (31%), as were 57 CD4+ T-cell epitopes (41%) and 54 CD8+ T-cell epitopes (69%).

According to the authors, "a virus can carry substantial sequence differences in some regions but still be recognized by the immune system if the virus retains sequence identity in regions including the immune epitopes," as the pandemic H1N1 virus does.

"Although T-cell responses do not prevent infection, they do contribute to the clearance of infected target cells," the investigators wrote, "and such pre-existing immunity may lead to a less severe course of disease" among infected patients.

The authors noted that, according to the Centers for Disease Control and Prevention, more than 1 million people in the United States were infected with pandemic flu between April 15 and July 24, 2009, which caused 5,011 hospitalizations and 302 deaths.

The National Institutes of Health provided funding for the study. The authors declared no individual conflicts of interest. ■

CDC Revises Flu Therapy Guide, Outlines Peramivir Use

Available data suggest pregnant women should receive prompt antiviral therapy.

BY JEFF EVANS
Elsevier Global Medical News

The Centers for Disease Control and Prevention updated its recommendations on early and late antiviral treatment during the 2009-2010 influenza season, and provided more guidance on the use of the investigational antiviral drug peramivir.

When to Start Antivirals

► **Patients with mild, uncomplicated illness who are not considered to be at increased risk of developing severe or complicated illness are not likely to benefit from antiviral treatment if started more than 48 hours after illness onset.**

Similarly, patients who are already recovering from influenza do not need antiviral medications. For patients who present within 48 hours of onset, clinical judgment should be used to decide if patients with mild or uncomplicated illness and no risk factors need antiviral drugs.

► **Antiviral regimens lasting 5 days are recommended for patients with confirmed or suspected 2009 H1N1 influenza who have severe, complicated, or progressive illness, or who are hospitalized.**

The 5-day treatment duration might be extended in some patients. Limited data from observational studies of hospitalized patients suggests that the initiation of antiviral treatment more than 48 hours after onset reduces mortality or duration of hospitalization in patients with prolonged or severe illness.

► **Promptly begin empiric antiviral therapy for patients with confirmed or suspected influenza who have an increased risk for complications, the CDC advised.**

These include children younger than 2 years of age, children and adolescents younger than 19 years of age who are receiving long-term aspirin therapy, adults aged 65 years and older, pregnant women, and individuals with certain medical conditions (asthma; neurological and neurodevelopmental disorders; chronic lung disease; heart disease; blood, endocrine, kidney, liver, or metabolic disorders; and a weakened immune system due to disease or medication).

► **Available data suggest pregnant women should receive prompt antiviral therapy.**

However, no clinical studies have assessed the safety and efficacy of oseltamivir (Tamiflu) or zanamivir (Relenza) for pregnant women. The systemic activity of oseltamivir makes it the preferred treatment for pregnant women. The agency also advises prompt antiviral treatment of women up to 2 weeks postpartum with suspected or confirmed 2009 H1N1 influenza (regardless of the pregnancy outcome), because anecdotal reports have suggested that they also may be at risk for severe complications and death.

Antivirals for Vaccinated Patients

A history of vaccination does not rule out influenza, the CDC advised, because vaccination for 2009 H1N1 or seasonal influenza is effective only after 2 weeks. In addition, each vaccine is not expected to provide protection against influenza viruses other than the targeted virus.

The agency recommends treating vaccinated patients as if they had not been vaccinated. People who are vaccinated with live attenuated influenza vaccines and who are given antivirals within 48 hours before or up to 2 weeks after vaccination might not develop immunity and should be revaccinated.

Oseltamivir Dosing for Infants

The CDC also updated its recommendations for dosing oseltamivir to pediatric patients.

For treatment purposes, infants younger than 1 year of age should receive 3 mg/kg of the drug twice per day. For chemoprophylaxis, those aged 3 months to less than 1 year should receive 3 mg/kg oseltamivir once per day.

Due to limited data, it is not recommended that the drug be given prophylactically to infants younger than 3 months unless the situation is judged to be critical. The weight-based dosing recommendations are not intended for premature infants.

Although oseltamivir dosing by weight is preferred for full-term infants younger than 1 year, it can be given according to age for treatment: 12 mg at 0-3 months, 20 mg at 3-5 months, and 25 mg at 6-11 months. Those doses should be halved for prophylaxis.

Peramivir Availability and Dosing

The Food and Drug Administration (FDA) approved the use of intravenously administered peramivir under an Emergency Use Authorization for hospitalized patients who have not responded to either oral oseltamivir or inhaled zanamivir antiviral drugs.

Peramivir also is indicated when patients are expected not to have a dependable or feasible route of delivery other than intravenous, or when a clinician judges intravenous therapy to be appropriate because of other circumstances. Pediatric patients may receive the drug if either of the first two criteria applies.

As of October, the FDA has received safety and efficacy data on the use of peramivir for 1,891 patients with acute uncomplicated seasonal influenza A. The drug has not been evaluated in hospitalized patients.

It is available from the CDC upon request by a licensed physician.

The FDA now recommends that adult patients with end-stage renal disease and a creatinine clearance of less than 10 mL/minute per 1.73 m^2 who are not receiving intermittent hemodialysis or continuous renal replacement therapy should receive 100 mg of peramivir intravenously on day 1, followed by 15 mg once daily.

The updated dosing regimen for pediatric patients who have that rate of creatinine clearance but are on intermittent hemodialysis varies according to age. From birth through 30 days, infants should receive 1 mg/kg peramivir on day 1, followed by 1 mg/kg 2 hours after each hemodialysis session on hemodialysis days only.

Following the same instructions, the dose increases to 1.3 mg/kg for infants 31-90 days old, 1.6 mg/kg for infants aged 91-180 days, 1.9 mg/kg for children 181 days to 5 years of age, and then back to 1.6 mg/kg for children aged 6-17 years.

Peramivir dosing for children who have a creatinine clearance of less than 10 mL/minute per 1.73 m^2 but who are not on intermittent hemodialysis or continuous renal replacement therapy follows the same initial dose on day 1 that is recommended for pediatric patients who are on intermittent hemodialysis. However, subsequent daily doses are lower, at 0.15 mg/kg from birth to 30 days, 0.20 mg/kg from 31 to 90 days, 0.25 mg/kg from 91 to 180 days, 0.30 mg/kg from 181 days to 5 years, and 0.25 mg/kg from 6 to 17 years. ■

The recommendations are available at www.flu.gov/individualfamily/prevention/medicine/antiviralsrecommend.html.

H1N1-Associated Invasive Pneumonia Is Increasing

BY ROBERT FINN
Elsevier Global Medical News

Investigators at the Centers for Disease Control and Prevention are seeing a "worrisome spike" in serious bacterial pneumonia associated with pandemic influenza A(H1N1) virus, Dr. Anne Schuchat said at a press briefing.

In the Denver metropolitan area, for example, there were 58 reported cases of invasive pneumococcal infections during the month of October. Over the last 5 years, there has been an average of only 20 cases each October.

Invasive bacterial pneumonia is normally seen in individuals older than age 65. But about two-thirds of the patients in the Denver area are between the ages of 20 and 59 years, Dr. Schuchat said. The majority of these patients had underlying risk factors in addition to H1N1 influenza.

"People at risk for invasive pneumococcal [infection] include adults with chronic health conditions like diabetes, asthma, emphysema, or other chronic lung diseases, chronic heart, kidney or liver disease, cancer and other immunosuppressive conditions like HIV," Dr. Schuchat said. "So a lot of adults are at higher risk for pneumococcal complications."

Studies show that only one-quarter of patients in these high-risk groups has received the highly effective and available pneumococcal vaccine. Adults typically require only one dose of the vaccine for lifetime protection.

In a person infected with influenza, an easing of symptoms followed by a sudden worsening is a key warning sign of a secondary bacterial infection. "We can see that in children or in adults," Dr. Schuchat said. "And it doesn't necessarily always mean bacterial pneumonia, but it very much can mean that."

STUDIES SHOW THAT ONLY ONE-QUARTER OF PATIENTS IN HIGH-RISK GROUPS RECEIVED THE HIGHLY EFFECTIVE PNEUMOCOCCAL VACCINE.

Other H1N1 influenza news discussed during the press briefing included confirmation that a physician in West Virginia appears to have come down with laboratory-verified H1N1 influenza twice over a period of 3 or 4 months. This is uncommon but not impossible, Dr. Schuchat said, and this case does not bear on the efficacy of the H1N1 virus vaccine, which is highly—but not 100%—effective.

To date 61.2 million doses of the vaccine have been made available, with an additional 7 million doses since Nov. 20. "We are expecting vaccination efforts to really step up as we come into December in concert with these improved supplies," Dr. Schuchat said.

The CDC continues to investigate adverse events associated with the vaccine. So far 94% of such reports relate to mild reactions such as soreness, tenderness, or injection-site pain. Anaphylaxis is not occurring more frequently than expected.

There have been 10 reports of possible cases of Guillain-Barré syndrome (GBS) associated with the vaccine, but not all of those have been confirmed. GBS is of particular concern because of a large number of cases associated with the 1976 swine flu vaccine. Dr. Schuchat said that 10 cases is a small number, given the large number of vaccine doses that have been administered. ■

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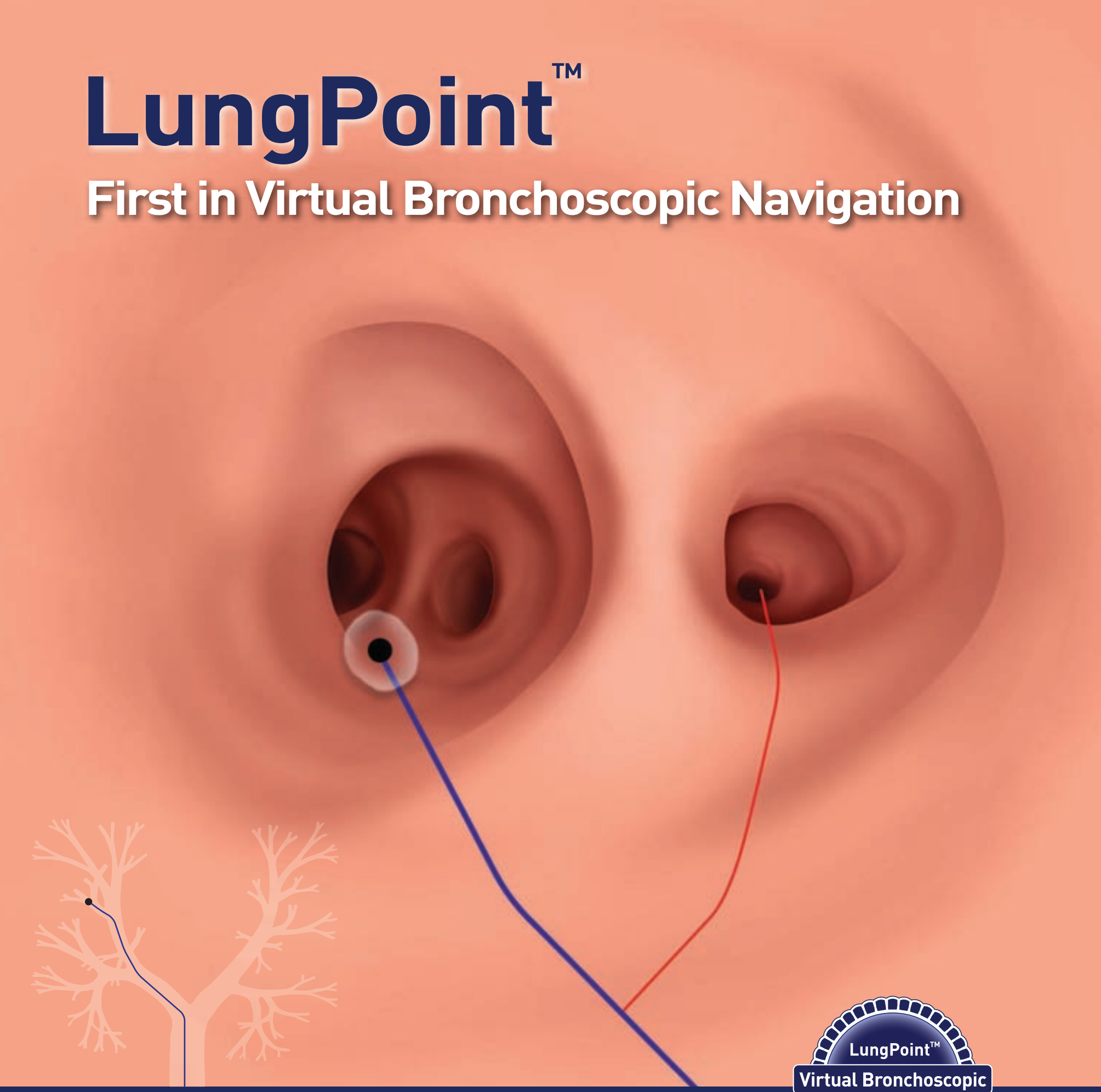

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Nasopharyngeal Swab Tests May Miss H1N1 Cases

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Antigen testing for the pandemic influenza A(H1N1) virus using nasopharyngeal swabs is not sensitive enough to be reliable in ICU patients, the experience at one busy inner-city New York hospital suggests.

Just 3 of 15 critically ill adults admitted to the ICU at Lincoln Medical Center in the South Bronx with H1N1 flu during the May-July outbreak had a positive nasopharyngeal swab. The other 12 tested positive only on bronchial washings or tracheal aspirates, Dr. Raghu S. Loganathan, FCCP, reported at CHEST 2009, the annual meeting of the American College of Chest Physicians.

Lincoln Medical Center has one of busiest emergency departments in the country, serving a minority population hard hit by 2009 H1N1. The hospital's experience during the first wave of H1N1 infection in late spring/early summer has led to a change in ICU practice at the hospital—one deserving of consideration elsewhere, said Dr. Loganathan, director of the medical ICU and stroke center there.

It can take 24-48 hours to obtain a lower respiratory tract specimen and diagnose H1N1 influenza in ICU patients. So now patients admitted to the Lincoln ICU with respiratory symptoms are placed in isolation with droplet and contact precautions at least until a lower respiratory specimen is obtained and the test results are known.

That's because during the May-July outbreak, when this practice was not yet in place, unprotected health care workers were exposed to the virus during that initial 24-48 hours—when the test results came back positive for H1N1, they required prophylaxis with oseltamivir (Tamiflu)—and their colleagues were placed at risk of infection, as were other patients in the ICU.

Just 3 of 15 critically ill adults admitted to the ICU had a positive nasopharyngeal swab.

DR. LOGANATHAN, FCCP

The 15 patients with H1N1 flu admitted to the ICU averaged 49 years of age, with an Acute Physiology and Chronic Health Evaluation score of 31. They were among 40 adults hospitalized with the infection during May-June, for a 37.5% ICU admission rate.

Thirteen of the 15 patients had at least one comorbid condition, including overweight or obesity in 9, diabetes in 8, and asthma or chronic obstructive pulmonary disease (COPD) in 7 patients. These comorbidity rates are substantially higher than those cited for ICU patients with H1N1 flu in other recent series from Mexico, Canada, Australia, and elsewhere in the United States, probably reflecting the demographics of the South Bronx, Dr. Loganathan observed.

Four ICU patients had normal chest x-rays. Eight had unilateral radiographic lung abnormalities, in contrast to the typically bilateral abnormalities seen in patients with seasonal flu. The radiographic findings consisted of alveolar consolidation in seven patients, interstitial infiltrates in two, and nodular infiltrates in two.

Lymphopenia was present in 10 of 15 patients, with a median value of 600 cells/mL. Elevated creatine phosphokinase was detected in nine patients, with a median value of 563 U/L. The median lactate dehydrogenase level in the 15 patients was 362 U/L, with 7 patients having a significantly elevated level indicative of hemolysis.

Twelve patients were placed on mechanical ventilation, including seven with acute respiratory distress syndrome. Ten patients had severe sepsis or septic shock. The mean ICU length of stay was 9.6 days. Four of the 15 patients died.

How do critically ill H1N1 flu patients compare with those requiring ICU care for seasonal influenza? Dr. Loganathan noted that a recent report (J. Clin. Virol. 2009 November;46:275-8) from the Mayo Clinic in Rochester, Minn., is illuminating on that score. The Mayo investigators reported on 103 ICU patients with seasonal influenza A and 8 with seasonal influenza B. The mean ICU length of stay for the critically ill patients with seasonal flu was just 3 days, compared with 9.6 days for the H1N1 flu patients, and the in-hospital mortality rate was 18.8% for the seasonal flu group, compared with 26% for the New Yorkers with severe H1N1 influenza. ■

HHS Funds Research for Hospital-Acquired Infections

BY JANE ANDERSON
Elsevier Global Medical News

The Department of Health and Human Services has awarded $17 million to fund research projects aimed at reducing central line–associated bloodstream infections and other hospital-acquired infections, including methicillin-resistant *Staphylococcus aureus*.

Nearly half of the funds will go toward financing a national expansion of the Keystone Project, which uses a checklist of evidence-based safety practices, staff training, careful measurement of infection rates, and teamwork-building tools for hospital staff to reduce the rate of central line–associated bloodstream infections (CLABSIs), according to the HHS.

The program, which has been implemented in more than 100 Michigan intensive care units, has saved more than 1,800 lives, more than $271 million in health care costs, and more than 140,700 excess hospital stay days in that state between 2004 and 2009, according to the Michigan Health and Hospital Association in Lansing.

In addition, data indicate that the CLABSI rates of hospitals participating in the Keystone program were consistently lower than the national average, the hospital association said in an October report.

Last year, the Agency for Healthcare Research and Quality (AHRQ) funded an expansion of the Keystone Project to 10 states. Now, with additional funding from the AHRQ and a private foundation, it is operating in all 50 states, the HHS said. The additional $8 million from the HHS will allow the program to expand to more hospitals, to extend to other settings in addition to intensive care units, and to broaden the focus to address other types of infections, the HHS said.

Dr. Thomas W. Barrett, a hospitalist at the Portland (Ore.) VA Medical Center, said in an interview that this type of implementation research is difficult to conduct because there are so many potentially confounding variables.

"This is a great step forward—it's very important for patient safety and patient care," Dr. Barrett said. "It's encouraging to see AHRQ take a great step in the right direction. I hope that since AHRQ is funding this, the level of rigor in the research will continue to improve."

To spend the remaining $9 million of the $17 million in new funding, the AHRQ said it collaborated with the Centers for Disease Control and Prevention to identify projects.

The projects chosen will focus on reducing *Clostridium difficile* infections through a regional hospital collaborative, reducing the overuse of antibiotics by primary care physicians treating patients in ambulatory and long-term care settings, evaluating two ways to eliminate MRSA in ICUs, and improving the measurement of the risk of infections after surgery.

Additional projects will attempt to identify rates of hospital-acquired infections, to reduce infections caused by *Klebsiella pneumoniae* carbapenemase-producing organisms by applying recently developed recommendations from the CDC's Healthcare Infection Control Practices Advisory Committee, to standardize antibiotic use in long-term care settings, and to implement teamwork principles for frontline health care providers, the AHRQ said. ■

Pages 6a-6d

New Test Sped Bacterial Infection Detection in Sepsis

BY JEFF EVANS
Elsevier Global Medical News

A testing method that uses positive blood cultures and an automated DNA-based polymerase chain reaction and microarray system accurately identified bacteria in sepsis much faster than a standard culture-based process.

The test identified bacterial species in patients with suspected sepsis with 95% sensitivity and 99% specificity, with a mean turnaround time of 23 hours—compared with 41.5-48 hours for the standard culture-based method, according to a report published online in the Lancet.

Although the sepsis assay is a "major advance" that encompasses the best of nucleic acid and standard culture-based methods, it is unknown yet whether determining the species of a pathogen 18 hours earlier than usual will "translate into demonstrable clinical benefit commensurate to the cost of undertaking the additional test," commented Dr. Shin Lin of Stanford (Calif.) University and Dr. Samuel Yang of Johns Hopkins University, Baltimore, who were not involved in the study (Lancet 2009 Dec. 10 [doi:10.1016/S0140-6736(09)61791-8]).

In the study, Dr. Päivi Tissari of the Helsinki University Hospital Laboratory and colleagues tested the Prove-it sepsis assay, manufactured by Helsinki-based Mobidiag, against standard blood culture and pathogen identification. The analysis included 3,318 blood samples from patients with suspected sepsis at two large academic medical centers (Lancet 2009 Dec. 10 [doi:10.1016/S0140-6736(09)61569-5]).

The assay identifies more than 50 species of gram-positive and gram-negative bacteria that cause most cases of sepsis.

A total of 2,107 blood culture samples tested positive, including 1,807 covered by the sepsis assay. The investigators compared DNA sequences of topoisomerase and 16S rRNA genes and original microbiological laboratory data for samples when the results of the assay and standard blood culture method were not the same.

WILL DETERMINING THE SPECIES OF A PATHOGEN 18 HOURS EARLIER THAN USUAL TRANSLATE INTO CLINICAL BENEFIT?

For organisms that could be detected with the sepsis assay, the results of the assay were between 93% and 100% concordant with the results of blood culturing for all species except one. The assay identified 133 of the 163 coagulase-negative staphylococci that were identified through blood culture.

False-positive results were identified in 52 of the 3,318 samples put through the assay. Those 52 false positives included 34 that were excluded due to contamination or software failure, 11 with more bacterial species detected than with conventional blood culture, 3 with *Staphylococcus epidermidis* reported instead of coagulase-negative staphylococci, 3 attributed to cross-hybridization between species, and 1 sample in which the assay also detected *Bacteroides fragilis*.

False-negative results occurred in 34 samples due to inadequate sensitivity for certain species, and in 60 samples because the sepsis assay did not detect all the bacteria it should have. The assay also had difficulty in resolving species in polymicrobial samples.

The median difference in turnaround time between the Prove-it assay and the reference method for 39 samples was 18 hours 19 minutes (range of 17 hours 29 minutes to 43 hours 8 minutes).

The assay provided 100% sensitivity and specificity for methicillin-resistant *Staphylococcus aureus*, although it is the only type of antibiotic resistance testing that can be performed with the assay, unlike standard biochemical analyses.

"Taking these features into account, the Prove-it sepsis assay cannot replace standard methods but could have a role alongside them," Dr. Lin and Dr. Yang wrote.

Five of the investigators are employees of Mobidiag, which provided the equipment and reagents for the Prove-it sepsis assay. None of the other researchers had conflicts of interest to declare. Dr. Lin and Dr. Yang had no conflicts of interest to report. The study was performed without outside funding. ■

Dr. Jeana O'Brien, FCCP, comments: *Use of the Prove-it system for identification of bacteria from positive blood cultures allowed identification of the specific pathogen in all but 14% of cases. A clinical sensitivity of 95% with a specificity of 99%, a false-positive rate of 1.6% and false-negative rate of 3% provides the clinician with strong support for safely narrowing antibiotic coverage. In the study, pathogens were identified an average of 18 hours earlier than conventional methods. Although antibiotic resistance testing is not generally available, the assay can detect MRSA with 100% sensitivity and specificity. Given the frequency of empiric coverage for this pathogen, the ability to narrow or add coverage is important. As with many new technologies, this assay is expensive. Whether the cost will be supported with improved patient outcomes remains for future studies. Factors such as difficulty with variable DNA extraction efficiency and potential for contamination must also be considered, especially outside of the research setting.*

Comprehensive Effort Can Boost VTE Prophylaxis Results

BY SUSAN BIRK
Elsevier Global Medical News

ROSEMONT, ILL. — A multifaceted intervention enabled a large health system to increase compliance with evidence-based guidelines for venous thromboembolism prophylaxis, according to Dr. Valerie Allusson, director of inpatient medicine services at Atlantic Health, Morristown, N.J.

Although the health system has not yet reached all of its quality benchmarks, compliance has risen substantially as the result of measures such as the creation of a physician order set and daily monitoring of compliance, Dr. Allusson reported at the Joint Commission national conference on quality and patient safety.

Atlantic Health's 504-bed Overlook Hospital was one of 41 hospitals to complete a 6-month Joint Commission–sponsored pilot study of VTE quality measures in 2006-2007. Following the pilot, Atlantic Health adopted VTE prevention and management as a systemwide quality goal and has spent the past 2 years focusing on VTE prophylaxis for medical and surgical patients at Overlook Hospital and the 629-bed Morristown Memorial Hospital.

VTE is 100 times more common in hospitalized patients than in the general population (Mayo Clin. Proc. 2001;76:1102), Dr. Allusson noted. She cited figures indicating that up to 2 million Americans experience VTE each year, and of these, 800,000 develop pulmonary thromboembolic syndrome (PTS), 600,000 develop pulmonary embolism (PE), and 300,000 die from PE (Lancet 1999;353:1386-9).

A baseline study of 100 randomly selected charts in one of Atlantic Health's medical units showed that only 39% of patients received VTE prophylaxis.

The system implemented a quality improvement initiative based on recommendations from the American College of Chest Physicians (Chest 2004;126:338S-400S) and the National Consensus Standards for the Prevention and Care of Deep Vein Thrombosis developed by the National Quality Forum and The Joint Commission.

Areas of particular focus were VTE risk assessment/prophylaxis within 24 hours of hospital admission and VTE written discharge instructions for patients on warfarin addressing follow-up monitoring, compliance issues, dietary restrictions, and potential drug reactions or interactions.

The system set a 6-month goal to conduct a VTE risk assessment and provide appropriate prophylaxis within 24 hours of hospital admission or surgery end time for 95% of all patients. A second 6-month goal was to reach 95% of patients who had "fallen through the cracks" and had been admitted without prophylaxis. "The goal was to get VTE assessment and prophylaxis ordered as often as possible at admission, but also on the floor, in transfer between units, or postoperatively," Dr. Allusson said.

Toward these ends, a multidisciplinary steering committee developed a VTE prophylaxis order set with a standardized risk assessment, contraindications for prophylaxis, and a checklist of appropriate options. It also developed a prototype daily VTE prophylaxis outlier list to indicate, by room, patients who were and were not receiving acceptable medications (including argatroban, fondaparinux, heparin, and low-molecular-weight heparin, and warfarin). A sticker was placed at the front of outlier charts to alert physicians about patients who had not received prophylaxis.

As of June 2009, the system had surpassed its target of 95% for prophylaxis in ICU patients (90%) and overlap therapy (82%), and was continuing to work on the remaining target of 95% for prophylaxis in medical/surgical patients (68%) and discharge instructions (79%).

In an interview, Dr. Allusson noted that the 95% target for prophylaxis in medical/surgical patients was ambitious considering the baseline rate of only 39%. The increase to 68% within 6 months represented significant progress, she said. The system also achieved a 5%-7.5% reduction in in-hospital mortality due to VTE during this time, but whether the decline was due to the VTE quality improvement project is not known.

Dr. Allusson attributed the progress to date in part to the frequent and routine sharing of data at every level of the organization, and to the multidisciplinary collaboration.

Efforts to systematize and streamline procedures related to VTE prophylaxis also helped. The new VTE prophylaxis order set, for example, allows physicians to document medications administered simply by checking the appropriate box. In addition, collaboration with information technology on such projects as the outlier report helped reduce the likelihood of human error.

In the future, the health system aims to develop a business plan for inpatient and outpatient anticoagulation management, include pharmacists in rounds to discuss anticoagulation issues and customized discharge instructions, create a unit performance tracking system, and establish mandatory prophylaxis order forms for all admissions. ■

Dr. Joseph Barney, FCCP, comments: *Applause for the motivation and efforts we read about from Dr. Allusson and all the staff involved in this project of process improvement. We live in a time of constant change in the delivery of health care in North America. Many health-care institutions have taken to globally reorganizing their measures for mortality review and changing the paradigm of implementing core measures of health care, such as DVT/VTE prophylaxis in efforts to become part of the solution to our growing problems with health-care costs and quality. Clearly, the model at Atlantic Health is an example of where we can go as institutions when there is collaboration and systematic oversight.*

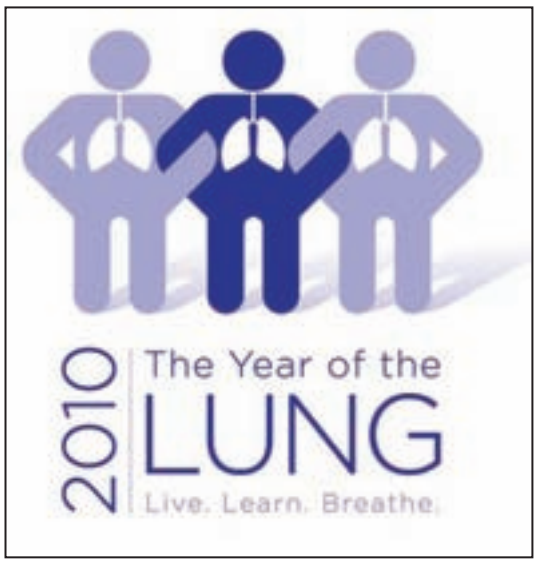
BY DR. KALPALATHA K. GUNTUPALLI, FCCP

PRESIDENT'S REPORT

Announcing 2010: The Year of the Lung

The announcement of life itself at birth by a loud cry has brought joy to millions from time immemorial. The tragedy of leaving this world with the "last breath" has also dramatized the lungs more than any other organ in the body.

Then why has it taken so long for this organ to get its fair shake in modern times?



The heart has earned its place as the "heart of the …," "at the heart of it all," "he has no heart," and "comes from the heart" in today's popular usage.

What about the lungs that supply oxygen to the heart? When the *New York Times* published public education material on different organs in the body (May 13, 2008), lungs were conspicuously missing!

Is it then, as practitioners of lung health, that we have not done justice to bring the organ we care for so much to the public notice?

Grim Statistics

The readers are familiar with these numbers—lung disease is very common and accounts for 19% of total deaths and 15% of disability-adjusted life-years in the world.

Tobacco-related diseases kill 5 million people worldwide and 1.5 million from lung cancer.

Despite the staggering numbers of 9 million new cases in 2007 and 0.7 million deaths a year from TB, no new drugs have been developed for TB since the 1970s, and the only vaccine available is a century old.

Pneumonia kills 2 million children under 5 each year; more than 250,000 asthma deaths per year are attributable to lack of treatment; and COPD will become the third most common cause of death worldwide in the near future, and, yet, it is frequently underdiagnosed.

Each year, 250,000 to 500,000 people die of seasonal flu in the world; and when new strains strike, the morbidity and mortality can be very high.

While the attention of the entire world community is focused on lungs, such as during the current H1N1 pandemic, it fades as soon as the threat is over. Lung disease exacts a tremendous financial burden on the patient, caregiver, and society.

Nearly half of the world's population breathes air that is polluted. Early lung disease detection methods, such as spirometry, are either not readily available or not utilized when available, making early detection a challenge.

Policies to regulate air quality are lagging. As of 2007, only 148 of the 193 World Health Organization member-states have ratified the Framework Convention on Tobacco Control.

2010: The Year of the Lung

That the year 2010 be designated as "The Year of the Lung" was proposed by the leading world respiratory associations to raise awareness of lung health and advocate for lung health globally.

The Forum of International Respiratory Societies (FIRS) has come together to declare **"2010: The Year of the Lung" (YOL).** FIRS comprises the American College of Chest Physicians (ACCP), American Thoracic Society (ATS), European Respiratory Society (ERS), Asociación Latinoamericana de Tórax (ALAT), Asia Pacific Society of Respirology (APSR), and International Union Against Tuberculosis and Lung Diseases (IUATLD).

As a group of respiratory and public health experts from around the globe, we want to engage our partners to raise the awareness of the deep impact of lung diseases worldwide. We eventually want policymakers to increase funding for lung disease research, enact smoking cessation legislation, support preventive measures, and support air quality legislation.

Objectives of 2010: The Year of the Lung

1. Promote global awareness of lung health issues and diseases.
2. Increase funding for lung health research.
3. Develop and implement tools to prevent lung disease and disability.
4. Diagnose and treat lung disease early in the course of illness.
5. Research new diagnostic tools and medicines to treat and cure lung disease.
6. Encourage programs that promote personal lung health (smoking cessation, lung hygiene, protective masks, flu vaccine).

The ACCP and 2010: The Year of the Lung

For the past 75 years, the ACCP has been committed to the prevention and treatment of diseases of the chest. This commitment, combined with the persistent efforts of 17,500 members in more than 100 countries, has helped disseminate ACCP's valuable lung health programs, initiatives, and education materials to reach countless patients and families in need.

The ACCP motto for 2010: YOL is *"From Prevention to Intervention."* As part of 2010: YOL, the ACCP will encourage worldwide lung health from "prevention to intervention," with core initiatives focusing on the areas of tobacco prevention, as well as the diagnosis and management of COPD and lung cancer.

The ACCP will coordinate with all national and international members to integrate YOL messages and promote YOL initiatives, including targeted Web pages that highlight ACCP clinical and patient tools and education material.

What Are We Doing Now?

► **Tobacco Prevention:** For the last decade, members of the ACCP (www.chestnet.org) and The CHEST Foundation (www.chestfoundation.org), the ACCP's philanthropic arm, have delivered The Foundation's Lung Lessons℠ program to schoolchildren across the United States and around the world. As part of the program, students learn how to keep their lungs healthy and about the dangers of tobacco use from ACCP members and other ambassadors of the College.

Each year, the ACCP organizes a special education program for schoolchildren in the host city during the College's annual meeting. The next Lung Lessons℠ school outreach event will take place in November 2010 in Vancouver, BC, Canada, coincident with the ACCP CHEST 2010 annual meeting.

Beyond the Lung Lessons℠ program, the ACCP and The CHEST Foundation will showcase and distribute the ACCP Evils of Tobacco, a culturally sensitive CD-ROM-based program that illustrates the severe hazards of tobacco use. The program, which includes talking points and material for presenters, has been developed in seven languages and has already been shared with thousands of children around the world.

The program "Ant E Tobacco," that includes a cartoon video, cartoon book, and coloring book for elementary schoolchildren, has been presented to more than 20,000 children in Texas.

► **COPD:** Through its regional COPD education program, *COPD: What Really Works? A Best Practices Workshop for Primary Care*, the ACCP will provide pertinent COPD screening, diagnosis, and treatment information to primary care health clinicians. In 2010, the programs will be hosted in 20 major markets around the country and will be a timely vehicle for spreading the YOL messages, especially as they relate to COPD.

► **Lung Cancer:** The ACCP publishes *Diagnosis and Management of Lung Cancer*, one of the leading evidence-based guidelines in lung cancer diagnosis, staging, and management. Throughout the 2010: YOL, the ACCP will build on the strong foundation of the guidelines to increase awareness regarding lung cancer prevention, diagnosis, and management. The ACCP also will provide education material for clinicians, patients, and patient families regarding critical care units and end-of-life and critical care family assistance.

I invite your active participation to take this campaign to your neighborhood and welcome any comments or suggestions. ■

COURTESY ACCP

ACCP President, Dr. Guntupalli, signs the declaration of "2010: The Year of the Lung," which was signed by the FIRS member organizations.

ACCP Online: Redesigned and Better Than Ever

www.chestnet.org

BY KEITH SENKOWSKI
Digital Media Solutions Manager

On January 2, 2010, the American College of Chest Physicians unveiled its redesigned Web site. More than 2 years in the making, the redesign combines best practices in interface design and member feedback, with the goal of providing a powerful resource for the members and others.

This combination provides a singular focus for the Web site, creating a polished showcase of most everything the ACCP has to offer.

Among the changes are the following:

- A clear organization of content into three major groups: News, Events, and Resources.
- A homepage that is always updated with the newest offerings from the ACCP.
- A vastly improved search engine, which makes finding relevant content easier than ever.
- Cross-site linking that puts related content at your fingertips.
- Thrice weekly updates of full news articles and daily updates of relevant news feeds.
- Regular blog postings, starting with *It Ain't Rocket Surgery*, written by *CHEST* Executive Editor Steve Welch.
- Monthly education content created by the ACCP NetWorks.
- New opportunities to earn CME through multimedia tools.
- A new events calendar that can be synced to your iCal®.

This is just a sample of the features the ACCP will be rolling out for its family of Web sites over the next year.

As your needs grow and change, this new site will allow the ACCP to meet those needs. Please contact the ACCP with your questions and concerns at techsupport@chestnet.org. ■

This Month in *CHEST*: Editor's Picks

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

TOPICS IN PRACTICE MANAGEMENT

- **Specialists/Subspecialists and the Patient-Centered Medical Home.** *By Dr. N. Kirschner; and Dr. M. S. Barr.*

ORIGINAL RESEARCH

- **Cardiovascular Events Associated With Ipratropium Bromide in COPD.** *By Dr. S. S. Ogale et al.*
- **Cardiovascular Safety of Tiotropium in Patients With COPD.** *By Dr. B. Celli et al.*

G/W EDITORIAL

- **Anticholinergic Drugs for the Treatment of COPD Are Safe … Are They?** *By Dr. K. F. Rabe.*

- **Use of Epidermal Growth Factor Receptor/Kirsten Rat Sarcoma 2 Viral Oncogene Homolog Mutation Testing To Define Clonal Relationships Among Multiple Lung Adenocarcinomas: Comparison With Clinical Guidelines.** *By Dr. N. Girard et al.*

- **Cost and Outcomes of Patients With Solitary Pulmonary Nodules Managed With PET Scans.** *By Dr. P. G. Barnett*

COMMENTARY

- **An Approach to Interventional Pulmonary Fellowship Training.** *By Dr. C. R. Lamb et al.*

www.chestjournal.org

NetWorks

Healthy Sleep in Teens and Antibiotics Delivery in CF

Allied Health

Project SIESTA Promotes Healthy Sleep Habits in Teens

Lata Casturi, RPSGT, a senior sleep technologist at the Baylor College of Medicine (BCM) Sleep Center and an Allied Health NetWork member, has been instrumental in guiding an extraordinary community service project that has brought a much needed awareness to the issue of healthy sleep habits for teenagers.

The impetus for the project originated when Anita Rao, a 7th grader, decided to do a science fair project about sleep. She approached Lata and, with input from Dr. Shyam Subramanian, FCCP, the Medical Director of the BCM Sleep Center, they formulated a comprehensive questionnaire that queried the bedtime and sleep habits of early teenagers, as well as their use of electronic media close to bedtime. Anita single-handedly coordinated the administration of this questionnaire to more than 100 middle-school students. The results showed a high prevalence of poor sleep hygiene, primarily due to a technology invasion of the bedroom environment in the early teenagers and a negative correlation with the daytime alertness of these students. Anita won first prize at the district science fair in recognition of her efforts.

Taking these results as a call to action, Lata suggested that Anita start a community education campaign to promote healthy sleep habits among teenagers. The results have been extraordinarily effective and rewarding. Under the mentorship of Lata, a team of six girls and two boys designated themselves as Project SIESTA. (Students Involved in the Education about Sleep hygiene for Teen Adolescents). In 4 months, the School Board endorsed Project SIESTA. The mayor of Houston, Bill White, declared October 30 as Healthy Sleep Day. The project team is promoting their message in many schools in the Houston area. The project has attracted national attention, and Anita Rao presented the findings of the group at the ACCP-Sleep Institute meeting at CHEST 2009.

Dr. Kalpalatha K. Guntupalli, FCCP, ACCP President and Chief of Pulmonary, Critical Care, and Sleep section at BCM, says, "It is very gratifying to note that the BCM Sleep Center has been a resource for the Houston community youngsters and schools in promoting healthy sleep habits early in life." The project is featured on an informational Web site at www.projectsiesta.com.

Chest Infections

Is It Just "the Bug" or Is There a Missing Link?

The 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team recently published its first report on the clinical characteristics of patients who were hospitalized with 2009 H1N1 influenza in the United States from April 2009 to mid-June 2009 (Jain et al. *N Engl J Med* 2009; 361(20):1935. Epub 2009 Oct 8). It is the first comprehensive report and suggests the following two interesting points:

A high percentage of hospitalized patients with H1N1 (~73%), specifically children (60%), had at least one underlying medical condition predisposing them to severe illness. This is in comparison with 31% to 43% of children who were hospitalized with seasonal flu as mentioned in their report. This observation suggests that this novel virus is not any more virulent than the seasonal flu or may even be less virulent, so far, considering the fact that severe illness is more likely with seasonal flu infection than with H1N1 if the individual/child is otherwise healthy.

The other important point is that hospitalized patients with H1N1 have a much higher prevalence of obesity, particularly morbid obesity (defined by BMI equal to or greater than 40 in adults only), compared with the general population. It was reported that morbid obesity prevalence was five times greater in these hospitalized patients than in the general population.

We will learn more about this H1N1 pandemic as more reports are published. In the meantime, early initiation of antiviral therapy should be prompt, along with supportive care, as initiation of the antiviral treatment within 2 days of the onset of influenza-like illness was the only treatment significantly associated with a positive outcome among hospitalized patients in this study. It is, nevertheless, time to acknowledge the significance of obesity not only as it relates to our health-care system but also to the current H1N1 epidemic and to question ourselves: Is it just "the bug," or is there a missing link?

Manish Joshi, MBBS, FCCP
Steering Committee Member

New Antibiotic Formulations

A pitfall in the treatment of chronic lung infection in cystic fibrosis and bronchiectasis is the inability of systemic antibiotics to penetrate into the affected areas. There is currently one US Food and Drug Administration-approved antibiotic formulation in cystic fibrosis, tobramycin solution for inhalation; inhaled colistin also has been used in the above diseases. Nebulization requires significant time, and intolerance, although uncommon, occurs in some patients.

However, recent research led to the development of antibiotic formulations for inhalation in both cystic fibrosis and bronchiectasis. These formulations are in different stages of clinical trials in both diseases and, if found effective, will be available for patient use. Most of these formulations consist of known antibiotics with improved efficient delivery or improved half-life, requiring fewer daily treatments.

Dry powder inhalation can lead to decreased time of administration. This method is used by tobramycin inhalation powder, which is currently in phase 3 trials (Geller et al. *Pediatr Pulmonol* 2007;42(4):307) and by inhaled ciprofloxacin, which is in phase 2 trials. An efficient nebulizer device has been used for aztreonam lysinate for inhalation and has successfully completed two phase 3 trials in cystic fibrosis and a phase 2 trial in bronchiectasis (Retsch-Bogart GZ et al. *Chest* 2009; 135(5):1223; and McCoy KS et al. *Am J Respir Crit Care Med* 2008;178(9):921). It is also used for nebulized levofloxacin in phase 2 trials. Another approach uses liposomes to deliver medication deep into the lungs, releasing it in a controlled fashion, leading to once-daily administration. It has been used by liposomal amikacin in a phase 2 trial. These medications could lead to a dramatically different paradigm of care for patients with bronchiectasis and cystic fibrosis, resulting in better control of chronic infection, fewer exacerbations, less lung function decline, and improved compliance.

Denis Hadjiliadis, MD, MHS, FCCP
Steering Committee Member

Note: Dr. Hadjiliadis has participated, or is currently participating, as a local principal investigator in multicenter clinical trials involving aztreonam lysine for inhalation (AZLI; Gilead Pharmaceuticals) and inhaled ciprofloxacin (Bayer Pharmaceuticals).

Clinical Pulmonary Medicine

Recognizing Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) has been defined as obesity (BMI >30) associated with hypoventilation (awake arterial carbon dioxide tension [$PaCO_2$] > 45) not attributed to other obvious causes, such as hypothyroidism, kyphoscoliosis, or severe COPD. The syndrome has been recognized for more than 50 years, but the significant morbidity and mortality associated with this syndrome has only recently been appreciated.

It is important to note that OHS is not obstructive sleep apnea (OSA). Though the majority of patients with OHS has OSA, the prognosis associated with the diagnosis of OHS appears to be significantly worse than that of OSA. Although comparative studies are lacking, reported mortality associated with OHS ranges between 3% at 18 months, in patients highly adherent to therapy, to 23% at 18 months, in patients not receiving appropriate therapy. This significant mortality associated with OHS far exceeds that associated with OSA.

Diagnosis of OHS requires a measurement of $PaCO_2$. At this time, direct measurement with arterial blood gas (ABG) testing is the accepted standard. Dr. Littleton and Dr. Mokhlesi compiled available epidemiologic data and report that patients with OHS tend to be severely obese (BMI equal to or greater than 40), hypersomnolent, and, if diagnosed with OSA, have an apnea-hypopnea index > 30 (*Clin Chest Med* 2009;30(3):467). The diagnosis of OHS should be sought after in this patient population; however, less obese patients and patients without OSA may also develop OHS.

The discomfort associated with ABG testing often causes physicians to seek alternate diagnostic options. Elevated serum bicarbonate levels and awake hypoxemia are strongly suggestive of OHS in the appropriate clinical setting but are not specific for the hypoventilation necessary to diagnose the disorder. Transcutaneous capnometry is a promising tool but, as of yet, has not been utilized in the diagnosis of OHS. Thus, given the lack of other reliable and readily available tests, ABG testing remains the gold standard for diagnosis and needs to be utilized.

Treatment of OHS is primarily aimed at treating the associated sleep-disordered breathing, usually present in the form of OSA.

Thus, continuous positive airway pressure (CPAP) is often part of the treatment plan. Since many patients with OHS require high CPAP pressures to address their OSA, CPAP intolerance becomes a significant concern. In that case, bilevel PAP therapy should be the next therapeutic consideration. Bilevel PAP may also be used to treat the hypoxemia that sometimes persists in these patients, despite adequate CPAP therapy for underlying OSA.

In patients with OHS without concomitant OSA, bilevel PAP may be used to address their sleep-related hypoventilation. ■

Philip Alapat, MD, FCCP
Steering Committee Member

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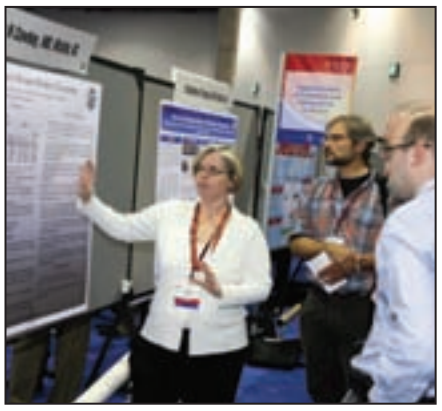
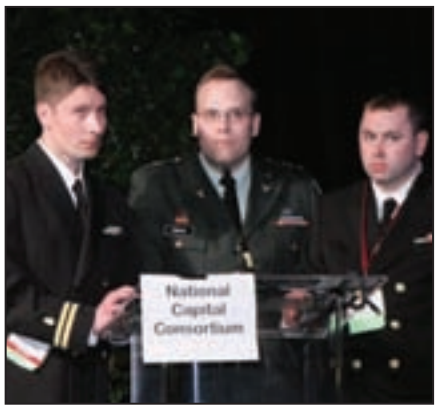
Snapshot of CHEST 2009

Pictures from CHEST 2009 are available for viewing and purchase at www.lagniappestudio.com/chest2009. Plan now to attend CHEST 2010, Oct 30 - Nov 4, in Vancouver, BC, Canada.

PHOTOS COURTESY ACCP



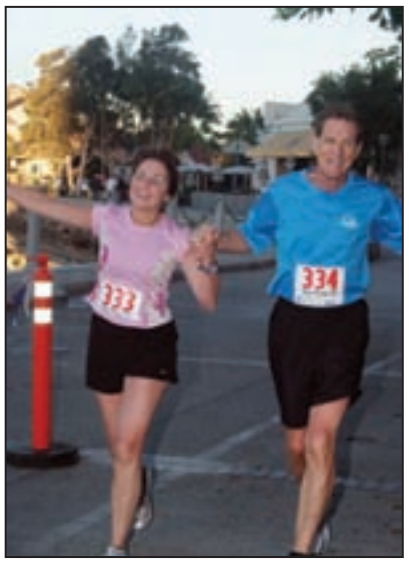


PCCU Lessons for January 2010

► **Respiratory Airway Medications: Select Toxicities and Drug Interactions**
By Raymond Y. Ho, PharmD

► **Biostatistics and Epidemiology for the Clinician**
By Dr. Arnold M. Schwartz, FCCP

PCCU
PULMONARY AND CRITICAL CARE UPDATE



A Resounding Success

The CHEST Foundation and the ACCP Industry Advisory Council 2009 Community Outreach Event

On Monday, November 2, 2009, more than 40 ACCP- and Ambassadors Group-member volunteers attended a training session to learn about the school and receive tips on working with children before boarding a bus to Sycamore Canyon Elementary School in Santee, California.

Located in a suburb east of San Diego, the school is uniquely designed wherein there are no interior hallways. Taking advantage of San Diego's mild climate, the 370 students, in grades preschool to grade 6, assemble each morning in the open courtyard of the school for the "Pledge of Allegiance" and general school announcements and proceed to their classrooms.

The superintendent and school principal greeted the volunteers at the general school assembly and then volunteers and children in grades 3 to 6 filed into their various classrooms to learn the facts about their lungs, asthma, and the dangers of smoking. A variety of educational tools were used to illustrate the anatomy of the lung, a healthy and diseased lung that could be pumped up so children could see the difference, and the cumulative effect of smoking one pack of cigarettes a week for 1 year in the notable "jar of tar." At the end of the lesson, the children were encouraged to sign the "I will never smoke" poster mounted on the wall of each classroom.

The ACCP Industry Advisory Council gave the Santee School District Foundation $10,000 to support educational programs for the children in the school district. This grant will be used to enhance after-school enrichment programs and purchase new laptop computers to replace the outdated computers in the elementary school classrooms. ■

COURTESY ACCP

Dr. Volkan Kara talks with students at Sycamore Canyon Elementary School about smoking's dangers.

FCCP CONNECTIONS

A Father and Son Story Not To Be Missed

BY PAMELA L. GOORSKY
Assistant Vice President, Editorial Resources

Dr. Ari Ciment, FCCP, sent a short e-mail to the ACCP just before CHEST 2009 asking if there would be any other father/son FCCP duos attending the CHEST meeting. After a little investigating, and speaking with the junior Dr. Ciment, I found that not only are he and his father an enthusiastic pair, but they have a unique story linking them to the ACCP in more ways than one.

As Ari took part in the Convocation Ceremony and became an FCCP at CHEST 2009, his father, Dr. Lawrence Ciment, FCCP, proudly watched from the audience. Years earlier, "Larry" Ciment trained in pulmonary/critical care with Dr. Marvin Sackner, FCCP, at Mt. Sinai Hospital in Miami Beach and was encouraged, during his fellowship, to attend the annual ACCP meetings.

Dr. Larry Ciment notes: "Those were the first of many ACCP meetings that I have attended and enjoyed. Although I remained in private practice and not in an academic position since that time, I found that reading *CHEST* and attending annual ACCP sessions helped me stay current in an ever-changing field.

"Realizing the tremendous value in personally seeing and hearing the state of the art at ACCP meetings, I insisted that my son develop the same appreciation early in his career!" he says.

So, with some "subtle" guiding from his father, Ari pursued an internal medicine route, and, eventually, a specialty in pulmonary/critical care. "I never felt pressured and chose the path because pulmonary/critical care is such a wide-ranging field. At the same time, I noticed from my professors at Rush Medical School that the pulmonary doctors were often the strongest all-around doctors, given their background in critical care, which prepared them as mini-specialists in each organ system."

Then, when Ari was a third-year medical student, his world came to an abrupt halt. "I vividly recall the phone call that night in 2002 when my father told me that chances were that he had less than a year to live," Ari relates. With a finding of multiple bilateral pulmonary nodules, suggestive of metastatic lung cancer (a nonsmoker, too), the senior Dr. Ciment waited for the pathologist's report. Ari was able to "weasle" his way into the frozen section room as the pathologist examined his father's slide.

He continues, "I reminded the pathologist of all the possible benign diagnoses. The pathologist squealed, 'I'm sorry son, but this looks like metastatic adenocarcinoma of the lung.' At this point, I still didn't give up and said, 'But the epithelium does look unusual for lung cancer.' He replied that there did seem to be some elements that resembled the salivary tissues. A light-bulb went off in my head, and I joyfully exclaimed, 'Perhaps this is a remnant of a somewhat benign jaw tumor my father had 29 years before?' The pathologist looked at me and incredulosuly remarked, 'I'll keep that in my differental diagnosis.'" Delivering his first-ever diagnosis of lung cancer to a patient, Ari had to disclose the findings to his own father.

But wait … there is more to this story.

As Ari tells it, at the postpathology review with the "gray-haired" chief pathologist who systematically reviewed all slides for a final diagnosis, an unbelievable thing happened. The pathologist noted cells typical of metastatic adenocarcinoma of the lung, but he then continued, **"But upon closer review, I haven't seen this tumor but one other time, 29 years ago when, as a chief resident here at Mount Sinai, I made the diagnosis of ameloblastoma in your father!** If he lived with it for 29 years, there is no reason to believe he won't live with it for another 29 years."

COURTESY ACCP

The father/son duo of Ari Ciment, MD, FCCP, and Lawrence Ciment, MD, FCCP.

The father and son together submitted the case report to *CHEST*, and it was published in April 2002 (*CHEST* 2002;121[4]: 1359-1361). Dr. Larry Ciment is alive and well today.

In ending my conversation with Ari, I asked him why he decided to become an FCCP, just as his father did years ago. He replied, "I believe that in order to excel in his field, I have to be involved in the society that harbors the top clinicians and educators of our era." Thank you, Drs. Ciment! ■

CHEST Physician Welcomes New Editorial Advisory Board Members

Dr. Joseph Barney, FCCP, is Assistant Professor, Pulmonary and Critical Care Medicine, at the University of Alabama at Birmingham (UAB), Birmingham, AL. He is the Director of the Department of Resuscitation at UAB and the Associate Director of the Medical Intensive Care Unit at the University of Alabama. Dr. Barney is also the Director of the Multidisciplinary Sarcoidosis Clinic at The Kirklin Clinic at UAB. He serves as core clinical faculty in the Department of Medicine at UAB, and he is intimately involved in resident and fellow training. Among his clinical and research interests are sarcoidosis, lung transplantation, interstitial lung diseases, and critical care medicine.

DR. JOSEPH BARNEY, FCCP

Dr. Jun R. Chiong, FCCP, is an Associate Professor of Medicine and the Medical Director of the Cardiomyopathy Program at Loma Linda University, Loma Linda, CA. Dr. Chiong completed his residency at the University of Illinois at Chicago Medical Center, Chicago, IL, and is currently doing his fellowship in cardiology at the University of Florida Health Science Center in Jacksonville, FL, serving as Chief Fellow during his final year. He was elected Chair of the ACCP Cardiovascular and Surgery NetWork for 2010. He is a recipient of two Young Investigator Awards, one from the ACCP and the other from the Florida Chapter of the American College of Cardiology.

DR. JUN R. CHIONG, FCCP

Dr. Stephen K. Field, FCCP, is a specialist in respiratory medicine and a Clinical Professor in the Department of Medicine, Division of Respiratory Medicine, at the University of Calgary, Calgary, AB, Canada. In addition to maintaining a large general respiratory consultative practice, he has also worked in the asthma/COPD and cystic fibrosis clinics at the university. He was a cofounder of the Calgary COPD & Asthma Program and the University of Calgary idiopathic pulmonary fibrosis/interstitial lung disease interest group. He has participated in numerous clinical trials in asthma, COPD, the role of gastroesophageal reflux in respiratory disease, lower respiratory tract infection, and mycobacterial disease, and he has published more than 60 papers on a variety of topics in respiratory medicine.

DR. STEPHEN K. FIELD, FCCP

DR. CARL A. KAPLAN, FCCP

Dr. Carl A. Kaplan, FCCP, is a Professor of Internal Medicine at Saint Louis University School of Medicine Health Science Center in the Division of Pulmonary, Critical Care, and Sleep Medicine, St. Louis, MO, where he is the Associate Director of the Fellowship Program. He is the Medical Director of Respiratory Care and Bronchoscopy Services at Saint Louis University Hospital, in addition to being the Director of the Interventional Pulmonary and Procedural Services and Minimally Invasive Thoracic Oncology Program. Dr. Kaplan is the Chair of the ACCP Respiratory Care NetWork Steering Committee and member of the ACCP-Critical Care Institute, and he is past Chair of the Critical Care NetWork Steering Committee. His interests are in the areas of critical care medicine, mechanical ventilation, respiratory care, bedside ultrasound and echocardiology, and medical education.

DR. JEANA D. O'BRIEN, FCCP

Dr. Jeana D. O'Brien, FCCP, is the Medical Director, Respiratory Care Department, Chief Medical Information Officer, and a practicing pulmonary/critical care medicine physician for Scott & White Healthcare in Temple, TX. Dr. O'Brien is in her first year as ACCP Governor for Texas. She is also past Chair of the ACCP Scientific Presentations and Awards Committee, past Chair of the Clinical Pulmonary Medicine NetWork, and a current member of the Respiratory Care NetWork Steering Committee and the Ethics Committee. Dr. O'Brien's interests are in health-care information technology, general pulmonary medicine, teaching in the ICU, and respiratory care. ■

New Editor and Deputy Editor Announced for Pulmonary Perspectives

Dr. Marilyn Foreman, FCCP, is the new Editor for Pulmonary Perspectives. She is an Associate Professor of Medicine at Morehouse School of Medicine in Atlanta, GA. Dr. Foreman is a Fellow of the ACCP and has participated in the ACCP as a member of the CHEST Program Committee, the Basic Science Subcommittee, the Scientific Presentations and Awards Committee, and the Cultural Diversity in Medicine NetWork Steering Committee. At Morehouse School of Medicine, Dr. Foreman has held a variety of administrative and supervisory roles in the Department of Medicine. Though she continues to participate in resident education, her primary focus is research on the genetics of COPD and tobacco-related health disparities, serving as a PI on several associated research trials and grants.

DR. MARILYN FOREMAN, FCCP

Dr. Loren Harris, FCCP, is the new Deputy Editor for Pulmonary Perspectives. He is Chairman of the Department of Surgery and the Director of the Division of Thoracic Surgery at Richmond University Medical Center in Staten Island, NY, and an Associate Professor of Surgery at New York Medical College. He has a multitude of national and international publications and presentations and is an investigator in several ongoing multicenter trials within the field of thoracic oncology. Dr. Harris is a Fellow of the ACCP and Vice-Chair of the ACCP Marketing Committee. He is a member of the advisory board of the American Cancer Society, Staten Island Region and continues to participate in several outreach programs on Staten Island for smoking cessation and lung cancer awareness education.

DR. LOREN HARRIS, FCCP

▶ **Special Note:** The ACCP would like to acknowledge Dr. Gene Colice, FCCP, for 3 years of outstanding service as Editor of Pulmonary Perspectives. The articles that he secured for publication in this section of *CHEST Physician* have been of great interest to our readers, and it is no small task to get a 1,400-word paper from an expert in the field each and every month.

Thank you for a job well done, Dr. Colice! ■

PRODUCT OF THE MONTH

CHEST Soundings—CHEST 2009 Symposia Executive Summaries

These executive summaries provide expert reviews and highlights on clinical information presented during select sessions at CHEST 2009.

These resources present various hot-topic medical issues relevant to your clinical practice and the care you provide to your patients. Included in each summary are references to additional relevant information that can add to your educational experience.

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.

After you view or read the available summaries, you may claim credit via the ACCP continuing medical education site at https://accp.chestnet.org/loginWA/LoginDispatchAction.do?wa=cme3.

We look forward to your participation, your responses, and your reactions. Welcome, and enjoy the activities and resources available exclusively from the ACCP. ■

Awards and Honors Presented at the 2009 Convocation Ceremony

▶ **College Medalist Award**
Richard S. Irwin, MD, Master FCCP
▶ **Presidential Citation Honor Lecture**
Stephanie M. Levine, MD, FCCP
▶ **Roger C. Bone Memorial Lecture**
J. Randall Curtis, MD, MPH, FCCP
▶ **Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation**
Nicholas S. Hill, MD, FCCP
▶ **Pasquale Ciaglia Memorial Lecture in Interventional Medicine**
Ko-Pen Wang, MD, FCCP
▶ **Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture**
Mark J. Rosen, MD, FCCP
▶ **Master Fellow Award**
Richard S. Irwin, MD, Master FCCP
Dario Olivieri, MD, Master FCCP
▶ **Alfred Soffer Award for Editorial Excellence**
Loren J. Harris, MD, FCCP
Glenn S. Tillotson, PhD, FCCP
▶ **Alton Ochsner Award Relating Smoking and Health**
Steven A. Belinsky, PhD
▶ **Canadian Thoracic Society Christie Memorial Lecture**
Arthur S. Slutsky, MD
▶ **The CHEST Foundation Clinical Research Award in Women's Health**
Ghada R. Bourjely, MD, FCCP
▶ **CTS/Institute of Circulatory and Respiratory Health Distinguished Lecture in the Respiratory Sciences**
James G. Martin, MD
▶ **Roger C. Bone Advances in End-of-Life Care Award**
Graeme Martin Rocker, MBBCh, FCCP
▶ **American College of Chest Physicians and The CHEST Foundation Grants in Venous Thromboembolism (VTE)**
Elie A. Aki, MD, PhD, MPH
Timothy A. Morris, MD, FCCP
▶ **Association of Specialty Professors and The CHEST Foundation of the ACCP Geriatric Development Research Award**
Kathleen M. Akgun, MD
▶ **The CHEST Foundation and the LUNGevity Foundation Clinical Research Award in Lung Cancer**
Johann C. Brandes, MD, FCCP
▶ **Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency**
Robert M. Reed, MD
▶ **The CHEST Foundation California Chapter Clinical Research/Medical Education Award**
Viswam S. Nair, MD
▶ **Third Eli Lilly and Company Distinguished Scholar in Critical Care Medicine Award**
Steven Q. Simpson, MD, FCCP

D. Robert McCaffree, MD, Master FCCP Humanitarian Award Recipients

$15,000 Project Development Grant Recipients

▶ **Nicola A. Hanania, MBBS, FCCP**
Annoor Sanatorium for Chest Diseases
Mafraq, Jordan
▶ **Stephen M. Winter, MD, FCCP**
Sustainable Health Promotion for the Indigenous Populations of the Northern Amazon Basin
Iquitos, Loreto, Peru

$5,000 Humanitarian Award Recipients

▶ **Henri G. Colt, MD, FCCP**
Community-Based Educational Program for Lung Cancer Awareness and Smoking Cessation
LaPaz, Sucre, and Cochabamba, Bolivia
▶ **Don Hayes, Jr., MD, FCCP**
University of Kentucky Salvation Army Pulmonary Clinic
Lexington, Kentucky
▶ **Subhakar Kandi, MD, FCCP**
Care and Support Foundation for Children
Hyderabad, Andra Pradesh, India

$5,000 Ambassadors Group Humanitarian Award

▶ **Martin L. Bauer, MD, FCCP**
Child Care and Conference for Parents Support Group of the Arkansas Center for Technology-Dependent Children
Little Rock, Arkansas

Sponsored Courses

January 28 - 31
Sleep Medicine 2010
Scottsdale, AZ

April 30 - May 2
Ultrasonography: Fundamentals in Critical Care
Austin, TX

August 25 - 28
Guidelines International Network Conference 2010
Chicago, IL

August 27 - 30
ACCP Pediatric Pulmonary Medicine Board Review 2010
Orlando, FL

August 27 - 30
ACCP Sleep Medicine Board Review 2010
Orlando, FL

August 27 - 31
ACCP Critical Care Medicine Board Review 2010
Orlando, FL

August 31
Lung Pathology 2010
Orlando, FL

August 31
Mechanical Ventilation 2010
Orlando, FL

August 31
ABIM Critical Care Medicine and Pulmonary Disease SEP Modules
Orlando, FL

September 1 - 5
ACCP Pulmonary Medicine Board Review 2010
Orlando, FL

October 30 - November 4
CHEST 2010
Vancouver, BC, Canada

ACCP Simulation Center for Advanced Clinical Education
Northbrook, Illinois

February 12-14
Basic and Advanced Bronchoscopy Skills With a Focus on Endobronchial Ultrasound

February 19-21
Critical Care Bundle

February
METI iStan Course

March 26-28
Difficult Airway Management

May
Human Patient Simulator

June 11-13
Critical Care Bundle

July 23-25
Difficult Airway Management

June 25-27
Mechanical Ventilation

July 30 - August 1
Basic and Advanced Bronchoscopy Skills With a Focus on Endobronchial Ultrasound

September
Critical Care Echocardiography

Focused Pleural and Vascular Ultrasound

COPD: What Really Works?
A Best Practices Workshop for Primary Care

Coming to 20 US cities.
Learn more and register at www.chestnet.org/copdedu

AMERICAN COLLEGE OF CHEST PHYSICIANS
2010 EducationCalendar

Learn more about ACCP-sponsored and ACCP-endorsed educational courses.
www.chestnet.org/education/calendar.php
(800) 343-2227 or +1 (847) 498-1400

AMERICAN COLLEGE OF CHEST PHYSICIANS

Attendees Were "Winners All" at CHEST 2009

Our CHEST 2009 attendees were all winners, as they were the first to "Experience ACCP" and first to encounter the newly structured and named "Clinical Resource Center."

The attendees were rightfully awarded with innovations, education, and practice solutions, including robust presentations, hands-on educational exhibitor demonstrations, experts on-hand for discussions, new products and initiatives, and, of course, CHEST t-shirts.

Convocation brought forth award winners in medicine and science, as did The CHEST Foundation Awards Program.

THE ATTENDEES WERE RIGHTFULLY AWARDED WITH INNOVATIONS, EDUCATION, AND PRACTICE SOLUTIONS, INCLUDING ROBUST PRESENTATIONS.

And then, there were winners in several contests held during CHEST.

The following companies won the best educational activity in their cluster in the Clinical Resource Center:

▶ **Airways**
Merit Medical Endotek

▶ **Cardiovascular** (There was a tie.)
Actelion Pharmaceuticals US, Inc.
Gilead Sciences, Inc.

▶ **Critical Care**
Edwards Lifesciences

▶ **Professional Development**
The France Foundation

▶ **Sleep**
Philips Respironics

▶ **Telemedicine and E-health**
ACCP/HIMSS IT Showcase

The bingo winners at CHEST 2009 received a $75 ACCP educational product gift certificate:

▶ **CHEST Bingo (Monday)**
Sara Ghendehari, MD - Los Angeles, CA
Allen Goldberg, DDS - Frankfort, IL
Robert Goodman, MD - Los Angeles, CA
Fernanda Paulino, MD - Belo Horizonte, Brazil
Christopher Spradley, MD, FCCP - Temple, TX

▶ **COPD Bingo (Tuesday)**
Linda Tan, MD, FCCP - Loma Linda, CA
Alison Kole, MD, MPH - Los Angeles, CA
Abdul M. Memon, MD, FCCP - Louisville, KY
Bahman Saatian, MD - Rochester, NY
Anupa P. Nadkarni, MBBS - Houston, TX

▶ **PAH Bingo (Wednesday)**
John Baron, MD, FCCP - Geneva, OH
Jeffrey Rymuza, MD, FCCP - Warner Robins, GA
Goutham Dronavalli, MD, MBBS - Houston, TX
Patricia A. Smith, MSN - Gaines, MI
William Schoenfeld, MD - San Diego, CA

Bingo was supported by Actelion Pharmaceuticals US, Inc.; AstraZeneca LP; CSL Behring; Hill-Rom; KCI; Talecris Biotherapeutics; The CHEST Foundation; United Therapeutics and LungRx; and Wyeth Pharmaceuticals.

We had many abstract and case report winners, and you can view the names of these winners at www.chestnet.org/CHEST/program/about/winners.php.

Plus, our CHEST Challenge Championship awarded the grand prize to the National Capital Consortium team from Bethesda, MD.

Everyone who participated in the 2009 Walk/Run was a winner, and the best times in each of the many categories are far too numerous to list here.

We congratulate and thank everyone who participated. ■

Urine Test May Help Identify Kids With OSA

BY TERRY RUDD
Elsevier Global Medical News

Proteins detectable in urine may offer a relatively simple screening target to identify children with obstructive sleep apnea, a study of 120 children suggests.

Abnormal levels of at least three of four proteins identified by the researchers proved to be 95% sensitive and 100% specific for obstructive sleep apnea (OSA) in young children aged 2-9 years.

Up to 3% of children have obstructive sleep apnea, which is characterized by habitual snoring and partial or complete upper airway obstruction. Differentiating those children from the 10%-12% of children who have primary snoring, but not OSA, requires challenging and expensive overnight sleep studies.

"Development of noninvasive biomarkers capable of reliably distinguishing children with [primary snoring] from those with OSA would greatly facilitate timely screening and diagnosis of OSA in children," noted Dr. David Gozal, FCCP, of the pediatrics department at the University of Chicago and his associates (Am. J. Respir. Crit. Care Med. 2009;180:1253-61).

The researchers studied 90 children referred to a pediatric sleep medicine center in Louisville, Ky., for evaluation of habitual snoring and suspected sleep-disordered breathing. A total of 60 children met polysomnographic and clinical criteria for OSA, while 30 had primary snoring. The study authors also included as controls 30 children who didn't snore and had no history of chronic or acute disorders.

The investigators used two-dimensional differential in-gel electrophoresis to assess protein expression in urine and identify proteins that were altered in the children with OSA.

In children with obstructive sleep apnea, levels of 12 urinary proteins differed from those in children with primary snoring or in controls. The investigators focused on three proteins whose levels increased in OSA—uromodulin, orosomucoid-1, and urocortin-3—and one protein whose levels decreased, kallikrein-1.

Abnormal levels of two or more of these four proteins predicted OSA with 100% sensitivity and 96.5% specificity. Abnormal levels of at least three of the proteins produced 95% sensitivity and 100% specificity.

What may link the four proteins to OSA? "It is reasonable to assume that the intermittent hypoxia and globally increased oxidative stress and inflammatory processes activated by OSA may lead to mild renal dysfunction," the researchers noted.

Dr. Gozal serves on a Merck & Co. speakers bureau. Some of the other study researchers have received corporate funding to develop biomarker assays and to study pediatric sleep apnea. ■

Sleep Duration Associated With Type 2 Diabetes Risk

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

Sleeping more or less than 7-8 hours a night was associated with a significantly greater risk of developing type 2 diabetes or impaired glucose tolerance, in a 6-year study of 276 adults.

The results "concur with a growing body of epidemiological evidence showing a U-shaped relationship between sleep duration and body weight, type 2 diabetes, coronary heart disease, and all-cause mortality," wrote Dr. Jean-Philippe Chaput of Laval University, Quebec City, and his associates. The study is in press at Sleep Medicine (doi:10.1016/j.sleep.2008.09.016).

Among the 276 men and women (aged 21-64) in the current cohort study, 21% who slept an average of 6 hours or less a night and 19% of those who slept an average of 9 hours or more a night developed type 2 diabetes or impaired glucose tolerance (IGT) over a mean of 6 years, compared with 7% of those who slept an average of 7-8 hours a night.

After adjustment for confounding factors associated with sleep duration and/or type 2 diabetes/IGT, such as age, smoking habits, shift work, and vigorous physical activity, those who slept 6 hours or less a night had a 2.78 times greater risk of developing diabetes and those who slept 9 or more hours a night had a 2.54 times greater risk, compared with those who slept 7-8 hours; the differences were significant.

Continued on following page

Probable RBD Common in Patients With Parkinson's

BY SUSAN LONDON
Elsevier Global Medical News

SEATTLE — Half of patients with Parkinson's disease meet criteria for probable rapid eye movement sleep behavior disorder, according to findings using a new screening tool.

What's more, patients with probable rapid eye movement (REM) behavior disorder are more likely to have other sleep disorders as well.

Studies using polysomnography or history suggest that REM behavior disorder (RBD) is prevalent in the Parkinson's disease population, supporting the need for a screening tool, according to Dr. Rositsa Poryazova, a neurologist at the University Hospital Zürich.

Such a tool—the REM Sleep Behavior Disorder Screening Questionnaire—recently was developed and validated in Germany, she noted. But its performance among patients with Parkinson's disease is unclear.

Dr. Poryazova and her coinvestigators surveyed randomly selected patients who were members of the Swiss Parkinson Association, a national Parkinson's disease patient organization. The patients were asked to complete the questionnaire and to rate the frequency of sleep problems on scales ranging from 1 (never) to 5 (almost always). Dr. Poryazova presented the results at the annual meeting of the Associated Professional Sleep Societies.

Analyses were based on 417 patients who had idiopathic Parkinson's disease, she reported. Fully 50% had a score of 5 or higher on the questionnaire, meeting the criterion for probable RBD.

Compared with their counterparts without probable RBD, the patients with probable RBD had significantly higher Epworth Sleepiness Scale scores (10.7 vs. 9.5) and had had Parkinson's disease for a significantly longer duration (11.1 vs. 9.6 years). Age, sex, scores for activities of daily living, and a levodopa-equivalent dose of medication did not differ significantly between groups.

Overall, 57% of patients reported having at least one sleep problem often or almost always.

Patients with probable RBD had significantly higher mean frequencies than did patients without probable RBD of nearly a dozen sleep problems, including talking or crying (2.9 vs. 1.8), restless legs syndrome symptoms (2.5 vs. 1.9), cursing or violence (1.9 vs. 1.2), nightmares (2.4 vs. 1.6), and hallucinations (2.0 vs. 1.4).

Discussing the findings, Dr. Poryazova acknowledged that a limitation of the questionnaire is its self-reported nature. "[Input] from the bed partner was allowed but not required," she noted, as many patients simply did not have bed partners. Overall, about half of the patients used such input.

"Probable RBD in Parkinson's disease patients is associated with various sleep disorders leading to higher arousability and sleep fragmentation," she concluded.

"These disorders may play a role as a precipitating factor in the occurrence of RBD," she said. In addition, "the higher frequency of concomitant sleep disorders leading to sleep fragmentation may result in increased daytime sleepiness in patients with probable RBD."

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

Restless Legs Syndrome Less Common in African Americans

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Marked racial differences exist in the prevalence of restless legs syndrome among adults, findings from a new study indicate.

The racial differences also have a gender overlay: Among men attending a primary care clinic for a wide range of reasons, restless legs syndrome (RLS) was twice as prevalent in non-African Americans as in African Americans. Among women, however, the racial disparity was even more striking: RLS was four times as prevalent in non–African American as in African American women, after adjustment for potential confounders, Dr. Ammar Alkhazna reported at CHEST 2009, the annual meeting of the American College of Chest Physicians.

The overall prevalence of RLS in the primary care population was far higher than in previous studies.

DR. ALKHAZNA

Another noteworthy finding in the 190-patient study was that the overall prevalence of RLS in the primary care patient population, 23%, was far higher than in previous studies by other investigators, where rates of 3%-10% have typically been reported, observed Dr. Alkhazna of the University of Missouri, Kansas City.

"RLS is underdiagnosed," he said. "The literature tells us more and more that we as doctors don't do a particularly good job of detecting patients with RLS and treating them."

The 103 African American and 87 non–African American study participants were attending a hospital primary care clinic in a multiracial, low-income, medically underserved area of Kansas City. They were interviewed one on one by personnel trained to use the Johns Hopkins Telephone Diagnostic Interview, a validated tool with 91% sensitivity and 93% specificity for the diagnosis of RLS.

A definite diagnosis of RLS was made in 12% of African Americans, among both men and women. Among non-African Americans, the diagnosis of RLS was definite in 40% of women and 29% of men, with an overall rate of 36%.

The explanation for the gender difference in RLS among non-African Americans is unclear, the researcher said. However, women have higher rates of rheumatoid arthritis and iron deficiency, both of which are known risk factors for RLS.

Why the African American women did not have a higher rate of RLS than African American men also is unknown. ■

Continued from previous page

After adjustment for waist circumference, the increased relative risk for the groups who slept more or less than 7-8 hours remained significant. There were no sex differences in risk.

Referring to evidence suggesting that about 7-8 hours of sleep a night may be optimal in terms of preventing common diseases and early death, the researchers wrote that the results of their study lend "empirical support to other published reports that indicate the practice of good sleep hygiene is crucial … to achieve good health."

The authors cited National Center for Health Statistics data from 2004, indicating that 30% of adult men and women between ages 30 and 64 said they sleep less than 6 hours a night.

In explaining the results of the current study, the investigators noted that previous data have suggested that prolonged partial sleep deprivation could predispose people to abnormal metabolic regulation, including clinical diabetes, and that partial sleep restriction can cause alterations in metabolic and endocrine functions, such as insulin resistance and reduced carbohydrate tolerance.

The mechanism underlying the impact of too much sleep is more speculative, they wrote.

The subjects in the study were part of the Quebec Family Study, a study on the influence of genetics on the etiology of obesity, fitness, and cardiovascular and diabetes risk factors, in 1,650 people from 375 families. ■

Prophylactic Brain Irradiation Results Mixed in NSCLC

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — Prophylactic brain irradiation significantly reduces the likelihood of brain metastases in patients with non–small cell lung cancer, but offers no survival advantage and produces temporary declines in memory.

The lack of survival benefit runs contrary to a 5% improvement in survival observed with prophylactic cranial irradiation (PCI) in small cell lung cancer, in which the rate of brain metastasis is higher and PCI use is fairly common.

Among the 340 patients in the current phase III study, PCI significantly decreased the incidence of central nervous system metastases at 1 year, from 18% with observation alone after definitive lung therapy to 7.7% ($P = .004$).

However, disease-free survival was 56.4% with PCI and 51.2% with observation ($P = .11$); the overall survival rate was 75.6% and 76.9%, respectively ($P = .86$).

There was significantly greater deterioration in both immediate and delayed recall in the PCI arm, compared with the observation arm, Dr. Benjamin Movsas reported on behalf of the Radiation Therapy Oncology Group (RTOG) 0214 study investigators at the annual meeting of the American Society for Radiation Oncology.

These declines in memory were "subtle" and occurred early, but also appeared to recover over time. Notably, PCI's effect on memory did not translate into sustained lower quality of life at any of the time points evaluated, said Dr. Minesh Mehta, an oncology professor at the University of Wisconsin in Madison.

Immediate recall on the Hopkins Verbal Learning Test deteriorated 45% in the PCI arm vs. 13% in the observation arm at 3 months (P less than .0001), improving to 19% vs. 5% at 6 months ($P = .045$) and 26% vs. 7% at 12 months ($P = .03$).

All patients had stage III non–small cell lung cancer, and had completed a combination of chest radiation, chemotherapy, and/or surgery without progression. PCI was administered for about 10 minutes on 5 consecutive days for 3 weeks, totaling 30 Gy of radiation in 2-Gy units.

Prior studies in small cell lung cancer evaluated neurocognitive function in relatively small numbers of patients, from which it was concluded that there was no clear evidence of neurocognitive impairment with PCI, said Dr. Movsas, chair of radiation oncology at the Henry Ford Health System in Detroit.

However, a more recent randomized "sister" study of PCI in small cell lung cancer that was presented at the same meeting showed a significant increase in neurocognitive decline at 1 year in the higher-dose PCI arm, compared with the lower-dose PCI arm, he said.

Dr. Minesh Mehta, who was invited to discuss the RTOG 0214 study, remarked that the memory data were most intriguing, particularly the suggestion of recovery over time. A recent study also showed a similar biphasic pattern of memory recovery in patients who were treated with whole-brain radiation therapy, implicating an "early responding" cell population (J. Clin. Oncol. 2007;25:1260-6).

The lack of survival benefit runs contrary to a 5% improvement observed with PCI in small cell lung cancer.

DR. MOVSAS

Both investigators suggested that the current findings support the use of neuroprotective strategies in radiation patients. That could potentially include agents such as donepezil (Aricept) or radiation-sparing techniques, including sparing the hippocampus, which is involved in memory and is the site of only about 3% of brain metastases, Dr. Movsas said in an interview. RTOG 0614 (a phase III study) is testing the ability of memantine (Namenda) to reduce cognitive dysfunction from whole-beam radiation therapy.

Dr. Mehta noted that target accrual for the current study was 1,058 patients, but that it was forced to close early because of low accrual, resulting in a 50% loss of data on memory outcomes. He went on to note that the study population represents just 0.1% of the more than 50,000 stage IIIA/B non–small cell lung cancer patients who are diagnosed annually. Possible reasons for the low accrual could be lack of interest or faith in PCI for non–small cell lung cancer, concern about its toxicity, or lack of access by radiation oncologists to patients after thoracic radiotherapy.

"It is a severe indictment of the whole field," he said.

The study was supported by grants from RTOG and the National Cancer Institute. Dr. Movsas reported no disclosures. ■

Low-Risk Lung Lesions Studied

Volume-Doubling • *from page 1*

They conducted a population-based randomized clinical trial of 7,557 high-risk patients undergoing spiral CT in the Netherlands and Belgium to determine whether assessing the volume and the volume-doubling time of such nodules could be used as the main criteria for deciding on further action.

Nodules were considered benign if the volume was less than 50 mm^3; if the volume was 50-500 mm^3 but did not increase by 25% or more during the interval between scans; or if the nodules grew but the volume-doubling time was calculated to be 400 days or more, signaling slow growth.

Results of the first CT screen were negative for lung cancer in 5,987 subjects (79%) and positive in 119 (2%). The remaining 1,451 subjects with indeterminate results underwent repeat scanning 3 months later.

A total of 518 nodules in these subjects were found to have a volume-doubling time of more than 400 days. This was considered to be a negative result, and the subjects could avoid further work-up. In contrast, lesions that showed a faster doubling time were considered to be positive, and subjects with these lesions underwent further, usually invasive, assessment.

All the subjects were followed for another 2 years to track the development of cancer in any lesions. "We found that the chances of finding lung cancer on a CT scan at 3 months, 1 year, and 2 years after a negative first-round test were 0, 1 in 1,000, and 3 in 1,000, respectively," Dr. van Klaveren and his colleagues wrote (N. Engl. J. Med. 2009;361:2221-9).

The study results are important because "a validated methodology governing the way this kind of CT-screening work-up is performed and reported does not exist" yet, noted Dr. James L. Mulshine of Rush University Medical Center, Chicago, and Dr. David M. Jablons, FCCP, of the cancer center at the University of California, San Francisco, in an editorial accompanying the study.

"When participants who had nodules with slow volume-doubling time were considered together with subjects whose scans were classified as negative at the first screening, and the combined group was followed for 2 years, [only] 20 lung cancers were detected. Thus, a negative scan, which included the presence of nodules with a slow volume-doubling time, was associated with a point-estimate negative predictive value of 99.7%," Dr. Mulshine and Dr. Jablons wrote (N. Engl. J. Med. 2009;361:2281-2).

They added that "it is promising that a first-generation tool for the measurement of the volume of nodules can perform at the high level reported by van Klaveren et al.," and noted that newer scanners with even higher resolution have become available since this study began.

The study was supported in part by a grant from Roche Diagnostics and with computer software and work stations from Siemens Germany. Dr. van Klaveren reported receiving advisory board fees, lecture fees, and grant support from Eli Lilly & Co., Roche Pharmaceuticals, and Roche Diagnostics. Dr. Mulshine reported receiving consulting fees from Savara Pharmaceuticals and being an inventor on patents involving molecular methods of lung cancer diagnosis. ■

ADCIRCA® (tadalafil) Tablets
BRIEF SUMMARY
The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please review the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND USAGE
Pulmonary Arterial Hypertension
ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

CONTRAINDICATIONS
Concomitant Organic Nitrates
Do not use ADCIRCA in patients who are using any form of organic nitrate, either regularly or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway.
Hypersensitivity Reactions
ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIRCA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS
Cardiovascular Effects
Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention.
PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.
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 ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIRCA is administered, the possibility of associated PVOD should be considered.
There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension

Use with Alpha Blockers and Antihypertensives
PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are 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, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.
Use with Alcohol
Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.
Use with Potent CYP3A Inhibitors or Inducers
Co-administration of ADCIRCA in Patients on Ritonavir
In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Co-administration of Ritonavir in Patients on ADCIRCA
Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
Other Potent Inhibitors of CYP3A
Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADCIRCA.
Potent Inducers of CYP3A
For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.
Use in Renal Impairment
In patients with mild or moderate renal impairment
Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.
In patients with severe renal impairment
Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.
Use in Hepatic Impairment
In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B)
Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily ADCIRCA.
In patients with severe hepatic cirrhosis (Child-Pugh Class C)
Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA.
Effects on the Eye
Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. 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 rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors.
Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.
Hearing Impairment
Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.
Combination with Other PDE5 Inhibitors
Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.
Prolonged Erection
There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.
ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).
Effects on Bleeding
PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
• Hypotension • Vision loss • Hearing loss • Priapism
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.
Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients.
In the placebo-controlled study, the most common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥ 9% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2%

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Headache	15	32	42
Myalgia	4	9	14
Nasopharyngitis	7	2	13
Flushing	2	6	13
Respiratory Tract Infection (Upper and Lower)	6	7	13

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2% (cont)

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Pain in Extremity	2	5	11
Nausea	6	10	11
Back Pain	6	12	10
Dyspepsia	2	13	10
Nasal Congestion (Including sinus congestion)	1	0	9

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.
Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. 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 tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.
Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis
Nervous — Migraine, seizure and seizure recurrence, and transient global amnesia
Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion
Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of 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.
Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. 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 tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.
Urogenital — Priapism.

DRUG INTERACTIONS
Potential for Pharmacodynamic Interactions with ADCIRCA
Nitrates
Do not use ADCIRCA in patients who are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life–threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.
Alpha-Blockers
PDE5 inhibitors, including ADCIRCA, 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. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.
Antihypertensives
PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood–pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.
Alcohol
Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.
Potential for Other Drugs to Affect ADCIRCA
Ritonavir
Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.
Other Potent Inhibitors of CYP3A
Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA.
Potent Inducers of CYP3A
For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.
Potential for ADCIRCA to Affect Other Drugs
Cytochrome P450 Substrates
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).
Aspirin
Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.
P-glycoprotein *(e.g., digoxin)*
Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category B
Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.
Non–teratogenic effects
Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.
Nursing Mothers
It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.
Pediatric Use
Safety and effectiveness of ADCIRCA in pediatric patients have not been established.
Geriatric Use
Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.
Renal Impairment
For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.
In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.
Hepatic Impairment
Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

OVERDOSAGE
Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

Marketed by United Therapeutics Corporation, Research Triangle Park, NC 27709

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Important Safety Information

Adcirca should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure. If a patient experiences anginal chest pain after taking Adcirca they should seek immediate medical attention. Adcirca contains the same ingredient (tadalafil) as Cialis, which is used to treat erectile dysfunction (ED). The safety and efficacy of combinations of Adcirca with Cialis or other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended. Patients with a known serious hypersensitivity to tadalafil should not take Adcirca. PDE-5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing Adcirca, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of Adcirca to these patients is not recommended. The use of Adcirca with alpha blockers, blood pressure medications, and alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (fainting). Tadalafil is metabolized predominantly by CYP3A in the liver. Use of Adcirca with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on Adcirca therapy that require treatment with ritonavir, Adcirca should be discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with Adcirca, start Adcirca at 20 mg once a day. Use of Adcirca with potent inducers of CYP3A, such as rifampin, should be avoided. The use of Adcirca is not recommended for patients with severe renal or hepatic impairment. Please see full prescribing information for dosing recommendations for patients with mild to moderate renal or hepatic impairment. In rare instances, men taking PDE-5 inhibitors (including tadalafil) for ED reported a sudden decrease or loss of vision or hearing, or an erection lasting more than four hours. A patient who experiences any of these symptoms should seek immediate medical attention. The most common side effects with Adcirca seen in the PHIRST-1 clinical trial were headache, myalgia, nasopharyngitis, flushing, respiratory tract infection, extremity pain, nausea, back pain, dyspepsia and nasal congestion. For full prescribing information and/or patient information, visit http://www.ADCIRCA.com or call 1-800-545-5979. Version 29 September 2009

Please see brief summary of Prescribing Information on next page.

References: 1. Adcirca [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2009. **2.** Galiè N, Brundage BH, Ghofrani HA, et al, for the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119:2894-2903.

*In patients with PAH treated with Adcirca 40 mg at 16 weeks compared with placebo.