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MAYO CLINIC

Obstructive sleep apnea put patients younger than 65 at greater risk of atrial fibrillation, Dr. Virend K. Somers, FCCP, explained.

Atrial Fibrillation Risk Rises in OSA Patients

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

SCOTTSDALE, ARIZ. — Obesity and obstructive sleep apnea are independent risk factors for atrial fibrillation in patients younger than 65 years of age, but not in older patients, according to a retrospective cohort study of 3,542 people who underwent sleep studies at the Mayo Clinic in Rochester, Minn.

Heart failure was the only independent predictor of new-onset atrial fibrillation for people 65 years of age and older in the study, which followed patients a mean of 4.7 years after an initial polysomnography.

"The ability of sleep apnea to predict the development of atrial fibrillation was dependent on the age of the patient. If they were more than 65, and they were in sinus rhythm when you did the sleep study, they didn't get atrial fibrillation," Dr. Virend K. Somers, FCCP, a coinvestigator, said at a meeting on sleep medicine sponsored by the American College of Chest Physicians.

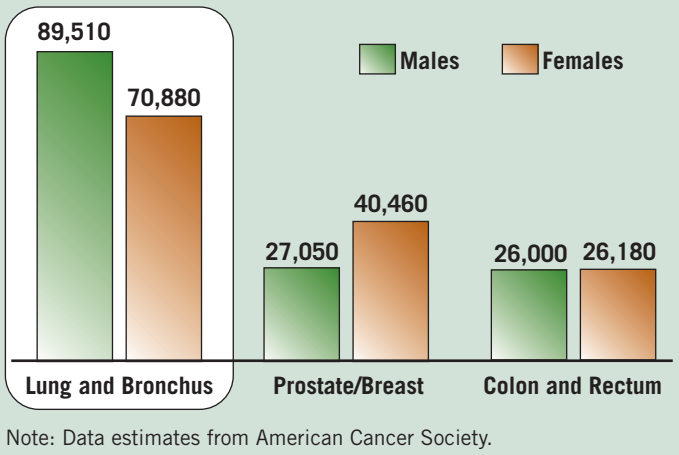
None of the patients reviewed had atrial fibrillation before or at the time of the screenings, conducted from 1987 to 2003, for possible sleep disorders. All told, 133 people developed atrial fibrillation at some point after undergoing polysomnography (J. Am. Coll. Cardiol. 2007;49:565-71).

Obstructive sleep apnea was diagnosed in 2,626 people (74%),

See **Atrial Fibrillation** • *page 13*

VITAL SIGNS

Lung and Bronchus Cancers Top the List of 2007 Estimated Cancer Deaths



Note: Data estimates from American Cancer Society.
Source: CA Cancer J. Clin. 2007;57:43-66

ELSEVIER GLOBAL MEDICAL NEWS

Proposed Federal Asthma Guidelines Emphasize Control

Highlight inflammation's critical role.

BY BRUCE K. DIXON
Elsevier Global Medical News

KEYSTONE, COLO. — Proposed federal guidelines for the diagnosis and management of asthma would place greater importance on asthma control in monitoring and adjusting treatment.

The 641-page document from the National Heart, Lung, and Blood Institute (NHLBI) underscores the importance of asthma control and further substantiates the critical role of inflammation.

The "Full Report of Expert Panel: Guidelines for the Diagnosis and Management of Asthma" cites emerging evidence for considerable variability in the pattern of inflammation, thus indicating phenotypic differences may influence treatment responses.

That proposed change "largely recognizes the fact that all the way from mild to severe asthma, the presence of neutrophilic predominance, rather than eosinophilic predominance, has been recognized in what may perhaps be 20% of asthmatics," said Dr. Harold S. Nelson, a member of the 18-member expert panel that drafted the guidelines for the NHLBI.

The guidelines were previously revised in 1996 and 2002.

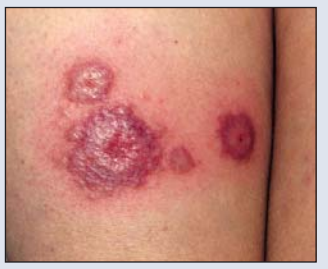
In addition, current asthma treatment with anti-inflammatory therapy, as recommended in the 1996 guidelines, does not appear to prevent disease progression, said Dr. Nelson, who is professor of medicine at the National Jewish Medical and Research Center in Denver.

"This remains an unsettled issue because of clinical trials suggesting that prolonging inhaled steroids reduces decline, but at least it's not as clear-cut as was once thought," he said at a meeting on allergy/clinical immunology, asthma, and pulmonary medicine.

The latest expert panel report

See **Asthma** • *page 11*

INSIDE



FDA Drops Two Indications for Ketek

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

The Food and Drug Administration has eliminated two indications for the antibiotic telithromycin and added a black box warning to its label stating the drug is contraindicated in people with myasthenia gravis.

Telithromycin, marketed by Sanofi-Aventis as Ketek, is no longer approved to treat acute bacterial sinusitis or acute bacterial exacerbation of chronic bronchitis. "FDA has determined that the balance of benefits and risks for Ketek do not support continued approval of Ketek for these generally nonserious and often self-limited illnesses," Dr. John Jenkins, director of the FDA's Office of New Drugs, said Feb. 12 in a telebriefing held to announce the revisions.

The ketolide antibiotic remains approved for treatment of mild to moderate community-acquired pneumonia (CAP) in patients aged 18 and over.

The label now includes a black box warning and contraindication about the risks of telithromycin in those with myasthenia gravis. Reports have included life-threatening respiratory failure associated with use of the drug in this population.

The warnings section of the label was also updated to include more information about other drug-specific adverse events, including visual disturbances and loss of consciousness. A bolded warning regarding the risk of potentially fatal hepatotoxicity, which was added in June 2006, will remain unchanged.

See **Indications** • *page 2*

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FDA Follows Panels' Advice

Indications • *from page 1*

In addition, an FDA-approved patient medication guide, developed with the manufacturer, now must be distributed with prescriptions and refills of telithromycin.

Although evidence for a favorable risk-benefit profile is weak for the sinusitis and bronchitis indications, "community-acquired pneumonia kills people," said Dr. John Bartlett, professor of medicine at Johns Hopkins University, Baltimore.

"And Ketek does have a clear advantage in the sense that it is highly effective, at least in the test tube, against the most resistant pneumococci, the most common cause of pneumonia," he said in an interview.

Dr. Bartlett was a member of an Infectious Diseases Society of America and American Thoracic Society joint committee that released guidelines on the management of CAP in adults shortly before the FDA's decision was announced.

Referring to the postmarketing reports of life-threatening hepatotoxicity associated with telithromycin, the IDSA-ATS guidelines note that the joint committee "is awaiting further evaluation of the safety of this drug by the FDA before making its final recommendation" regarding the drug's role in treating CAP (Clin. Infect. Dis. 2007:44:S27-72).

The label revisions reflect recommendations made at a joint Anti-Infective Drugs and Drug Safety and Risk Management Advisory Committee meeting in December 2006. The majority of the two FDA advisory panels recommended that based on the available data, including data collected since the drug was approved in 2004, the benefits of telithromycin did not outweigh its risks for the sinusitis and bronchitis indications.

FDA advisory panelists indicated, however, that the drug's benefits outweighed its risks in patients with CAP.

At the December meeting, the FDA reported that there had been 33 reports of exacerbations of the neurologic disease associated with telithromycin since 2004. These cases included 7 that were life-threatening and 12 cases in which patients required ventilation or intubation.

Also during the meeting, the FDA reported there were 12 cases of acute liver failure among 5 million U.S. prescriptions written from 2004 to 2006, resulting in a reporting rate of 23 per 10 million prescriptions.

Sanofi-Aventis will provide information on the revisions to health care professionals in a letter to health care providers, and have experts available to answer questions, by calling 1-800-633-1610 (option 1).

The revised label and other information is available at www.fda.gov/cder/drug/infopage/telithromycin/default.htm, and at www.sanofi-aventis.us/live/us/en/index.jsp. ■

Dr. Doreen Addrizzo-Harris, FCCP, comments: *Physicians need to weigh the risk versus benefit in each individual patient when choosing specific antibiotic regimens. They must be familiar with the complications in the drugs they use routinely and report any serious complications in a timely manner.*

IN THIS ISSUE

CHEST PHYSICIAN Is Online

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National Provider Identifier Sign-Up Deadline Is May 23

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

The clock is ticking for physicians to sign up for a National Provider Identifier, the new 10-digit number that will be used by Medicare, Medicaid, and many private health plans to process claims.

The deadline for registering for an NPI number is May 23. Physicians who are not using an NPI number after that date could experience cash flow disruptions, according to the Centers for Medicare and Medicaid Services.

Most health care plans and all health care clearinghouses must begin using NPIs to process physicians' claims in standard transactions by May 23. Small health care plans have another year to become compliant.

"The NPI is the new standard identifying number for all health care billing transactions, not just for billing Medicare or Medicaid," said Aaron Hase, a CMS spokesman. As of Jan. 29, more than 1.6 million NPIs had been assigned, according to CMS.

Physicians and other providers can apply for an NPI online or by using a paper application. Hospitals or professional associations can submit applications for several physicians in an electronic file.

A physician who submits a properly completed electronic application could have his or her NPI in 10 days. However, it can take 120 days to do the remaining work to use it, Mr. Hase said.

One thing to be aware of is that you may already have an NPI, because some large employers may have already registered their providers, Mr. Whitman said.

The next question is how widely CMS plans to disseminate the NPIs. CMS officials have said they are considering creating some type of directory of NPIs that could be available to physicians and office staff. ■

Physicians can apply for an NPI online at https://nppes.cms.hhs.gov or call 800-465-3203 to request a paper application.

FDA Wants Boxed Warning for Xolair

The Food and Drug Administration has requested that Genentech Inc. add a boxed warning to the labeling for omalizumab (Xolair) following new postmarketing reports of anaphylaxis occurring after administration of the drug.

Omalizumab has been on the market since 2003, and is indicated for use in patients aged 12 years and older with moderate to severe persistent asthma who are allergic to perennial aeroallergens and whose symptoms cannot be controlled with inhaled steroids. Omalizumab is a recombinant DNA-derived humanized IgG1 (kappa) monoclonal antibody that selectively binds to human IgE.

In clinical trials that included 39,500 patients, anaphylaxis occurred in approximately 0.1% of patients, generally within 1-2 hours of receiving a subcutaneous injection of the drug. The new reports, however, include patients who had delayed anaphylaxis—with onset even beyond 24 hours after administration.

The new warning also would emphasize that anaphylaxis can occur after any dose of omalizumab, even if there was no adverse reaction to a previous dose. For more information, go to www.fda.gov/cder/drug/infopage/omalizumab/default.htm.

—Nancy Walsh

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POINT/COUNTERPOINT

Are daily inhaled steroids appropriate for mild persistent asthma?

Daily ICS therapy may prevent airway remodeling.

BY DR. MARK S. DYKEWICZ, FCCP

Studies have shown that the regular use of inhaled corticosteroids significantly improves multiple outcomes in patients with mild persistent asthma (MPA), including asthma control, airway hyper-responsiveness and inflammation, and lung function.

We even have some evidence that regular inhaled corticosteroids (ICS) in MPA may reduce exacerbations and prevent decline in lung function.

The OPTIMA study found that regular ICS use in MPA, even in ICS-naïve patients, could significantly reduce severe exacerbations, improve asthma control, and improve other outcomes (Am. J. Resp. Crit. Care Med. 2001;164:1392-7).

The START study enrolled more than 7,000 MPA adults and children within 2 years of their asthma diagnosis. During this 3-year placebo-controlled trial, patients randomized to regular ICS had significantly fewer severe asthma exacerbations, more symptom-free days, and decreased need for rescue oral corticosteroids. They also had significant improvements in both pre- and postbronchodilator forced expiratory volume in 1 second (FEV_1), suggesting that early intervention with regular ICS can forestall decreases in lung function (Lancet 2003;361:1071-6).

The IMPACT trial, published in 2005, studied 225 adults with MPA who received intermittent short-course corticosteroids guided by a symptom-based action plan, either alone or with daily ICS (budesonide) or zafirlukast (N. Engl. J. Med. 2005;352:1519-28). After 1 year, the budesonide group had significantly better prebronchodilator FEV_1, better asthma control scores, more symptom-free days, and less airway hyperresponsiveness.

The authors suggested that it is possible to treat MPA with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen because they did not find a difference between groups in morning peak flow expiratory flows, postbronchodilator FEV_1, or exacerbations. However, morning peak expiratory flow likely is not a very useful end point in patients whose lung function is near normal to begin with.

IMPACT also had a substantially lower incidence of exacerbations in patients than did START or OPTIMA, likely too low to draw any conclusions. And it only included adult patients with a long history of asthma (17-21 years), a population in whom regular ICS may be less likely to preserve lung function.

Although further studies are needed, regular ICS treatment in MPA could also have an important beneficial impact on the economics of asthma, particularly if reduced exacerbations translate into less time off work and school and fewer hospital visits. An economic subset analysis of the START data concluded that even in children aged 5-10 years, regular ICS resulted in societal savings of $192 over 3 years, partly because caregivers had to take less time off from work (Pediatr. Allergy Immunol. 2006;17[suppl. 17];21-7).

Overall, the low doses of ICS needed to control mild persistent asthma are very safe. START did show a mild reduction in growth velocity for children receiving regular ICS, although it is unlikely that final adult height will be significantly affected.

Symptom-based intermittent corticosteroid treatment for MPA would require a very thorough, continuing assessment of asthma severity and control. In actual practice, both physicians and patients tend to underestimate asthma severity. Consequently, symptom-based intermittent treatment for MPA likely would lead to undertreatment of many patients whose asthma is actually more severe.

THERE IS INSUFFICIENT EVIDENCE TO ALTER THE WELL-GROUNDED RECOMMENDATION TO TREAT MPA WITH REGULAR INHALED CORTICOSTEROIDS.

In conclusion, there is insufficient evidence to alter the well-grounded recommendation to treat MPA with regular ICS. ■

DR. DYKEWICZ, *FCCP, is director of the allergy and immunology program at St. Louis University School of Medicine. He disclosed that he has received grants from and/or been a consultant/advisor to and/or been on the speakers bureau of AstraZeneca, Critical Therapeutics, GlaxoSmithKline, IVAX/Teva, Merck, Novartis/Genentech, and Schering-Plough. He owns no stock in any pharmaceutical company.*

ICS therapy on an as-needed basis is just as effective.

BY DR. TIMOTHY CRAIG

For patients with mild persistent asthma, inhaled corticosteroids taken on as as-needed basis are just as effective as daily therapy, much less expensive, and more in line with the way our patients are actually taking the drug.

And while the jury is still out on whether as-needed inhaled corticosteroids (ICS) positively affect airway remodeling, there is likewise little firm evidence that daily use is any more effective.

We treat mild persistent asthma (MPA) with regular ICS simply because our 1997 National Asthma Education and Prevention Program guidelines suggested that daily treatment might preserve lung function as well as relieve symptoms and prevent exacerbation. But this guideline change was based on only a very small number of studies, all of which were performed before the division of mild asthma into the two groups we now recognize: persistent and intermittent.

Let's examine some more recent data. IMPACT, for example, is often cited as evidence that regular ICS improves many outcomes for patients with MPA. But this study showed no significant differences in morning peak flow between any of the groups. There were no differences in asthma exacerbation rates, and no differences in the need for the addition of prednisone. While those on regular ICS did have more symptom-free days, the difference was very small—only about 26 days per year. And there were no differences on the asthma control questionnaire or in exacerbation rates over time.

Nor was there a difference in postbronchodilator forced expiratory volume, demonstrating that regular ICS did not significantly affect airway remodeling. Daily ICS seemed to have a positive effect on airway inflammation, with that group having fewer sputum eosinophils and lower exhaled nitrous oxide.

The START trial did show that patients with new-onset MPA could benefit from daily ICS therapy—but not very much. The difference in FEV_1 after 3 years of budesonide or placebo was only 1%—a finding that the investigator himself said could be attributed to the high rate of concomitant ICS use in the placebo group, which was allowed by study design (Chest 2006;129:1478-85).

The CAMP study examined daily low-dose budesonide in children with MPA. While patients in the budesonide group had better asthma control than did those taking nedocromil or placebo, there was still no significant change in FEV_1, suggesting once more that the daily ICS does not have an affect on airway remodeling (N. Engl. J. Med. 2000;343:1054-63).

IF OUR MAIN THRUST IN DAILY INHALED CORTICOSTEROID THERAPY IS TO PREVENT AIRWAY REMODELING ... WE ARE CLEARLY MISSING THE TARGET.

The CARE study looked at daily fluticasone compared with placebo in children at risk of developing asthma. The results of this 3-year trial were less than impressive for daily ICS, with just 1 less episode-free day (96 vs. 97), no change in hospitalizations or posttreatment lung function, and no benefit on airway remodeling (N. Engl. J. Med. 2006;354:1985-97).

If our main thrust in daily ICS therapy is to prevent airway remodeling and preserve lung function, we are clearly missing the target—possibly because only higher doses of ICS could bring about these kinds of changes. And high-dose ICS is not something we're ready to discuss.

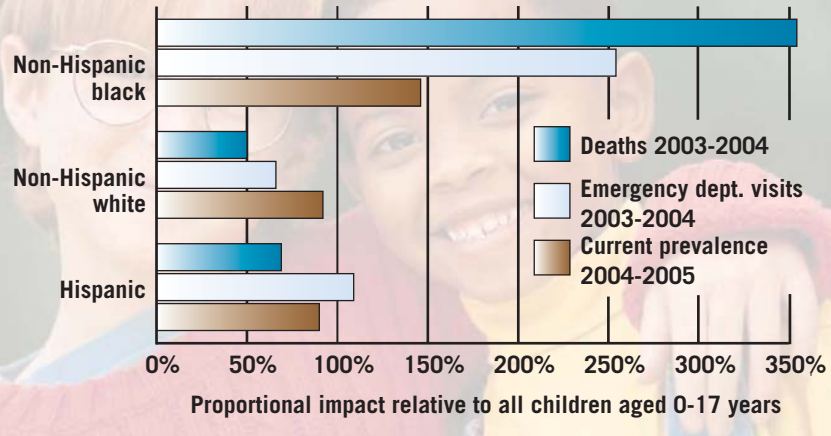
But ICS administered according to symptoms does fulfill our other asthma management goals, increasing control and quality of life, decreasing symptoms and mortality just as well as daily ICS, with some notable benefits.

In summary, as-needed treatment is less expensive than is daily treatment with ICS. It is associated with fewer side effects. And with as-needed therapy, you don't have the compliance worries that come with daily treatment. ■

DR. CRAIG *is the training program director of the allergy section and director of clinical allergy and respiratory research at Pennsylvania State University, Hershey Medical Center, Hershey, Pa. He disclosed that he has served on an advisory board for Sanofi-Aventis, and he has received grants from GlaxoSmithKline, Merck, Methapharm, Schering-Plough, and ZLB Behring. He owns no stock in any pharmaceutical company.*

DATA WATCH

Effects of Asthma Greater Among Non-Hispanic Black Children



Note: Proportional impact is calculated by dividing the percentage for each outcome among each race/ethnicity by the percentage for each outcome for all children 0-17 years of age.
Source: Centers for Disease Control and Prevention

Airborne Particulates Tied to Women's Cardiovascular Risk

BY MARY ANN MOON
Elsevier Global Medical News

Long-term exposure to fine particulate air pollution correlates with the rate of cardiovascular disease and CVD death in postmenopausal women, reported Kristin A. Miller of the University of Washington, Seattle, and her associates.

Older women who live in areas with high levels of fine particulate matter show a higher risk of cardiovascular events—MI, stroke, coronary revascularization procedures, and death from heart or cerebrovascular disease, the investigators said in the Feb. 1 issue of the New England Journal of Medicine.

Using data from the Women's Health Initiative (WHI) prospective cohort study, Ms. Miller and her associates evaluated exposure to particulate air pollution of less than 2.5 mcm in diameter in 65,893 subjects who were free of CVD at baseline. The women were aged 50-79 years at enrollment, and all lived within several miles of Environmental Protection Agency monitors that measured ambient community-scale air pollution. Most had lived in one place for 20 years or more.

A total of 1,816 women developed incident cardiovascular events during the study.

There was an estimated 24% rise in risk of a cardiovascular event and a 76% rise in risk of cardiovascular death with every increase of 10 mcg per cubic meter in fine particulate air pollution, the researchers said (N. Engl. J. Med. 2007;356:447-58).

For cerebrovascular disease in particular, there was a 35% rise in risk of stroke and an 83% rise in risk of stroke death with every increase of 10 mcg per cubic meter.

Adjustment for numerous CV risk factors, including exposure to environmental tobacco smoke, occupation, household income, diet, and medical history, did not alter the risk.

"We did not observe robust effects with other sizes of particulate matter or with other measured air pollutants," including sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone, Ms. Miller and her associates noted.

In an accompanying editorial, Douglas W. Dockery, Sc.D., of Harvard School of Public Health, Boston, and Dr. Peter H. Stone of Harvard Medical School, Boston, said this study's most important contribution may be that it "established a stronger statistical association between fine particulate air pollution and death from coronary heart disease than that found in earlier studies" (N. Engl. J. Med. 2007;356:511-3).

"A particularly appealing aspect of the design of the WHI study is the range of data collected on all subjects, including demographic and lifestyle characteristics," they added. ■

Lung Embolism Ruled Out by Multidetector CT Angiography

CHICAGO — It is safe to withhold anticoagulation therapy in patients with suspicion of pulmonary embolism on the basis of negative multidetector CT pulmonary angiography and venography, according to a study presented at the annual meeting of the Radiological Society of North America.

Venography or lower-limb ultrasound is a wise addition to the multidetector CT work-up.
DR. BRAUN

However, a small number of patients with negative multidetector CT (MDCT) pulmonary angiograms may have venous thrombosis, making venography or lower-limb ultrasound a wise addition to the work-up, said Dr. Petra Braun.

"We compared the multidetector CT with scintigraphy and lower-limb ultrasound and, in our opinion, the CT definitely makes it possible to exclude pulmonary embolism, and therefore you don't need other diagnostic tests for that," said Dr. Braun of the University Hospital La Fe, Valencia, Spain.

A total of 383 consecutive patients with suspicion of acute pulmonary embolism were studied prospectively with MDCT. In addition, ventilation-perfusion scintigraphy and lower-extremity sonography were performed, Dr. Braun explained during a poster session.

Patients with negative CT and without anticoagulation therapy underwent a 6-month follow-up to exclude recurrent pulmonary embolism or venous thrombosis.

A total of 156 patients had a positive MDCT, 224 had negative scans, and 3 had inconclusive results. In addition, five patients with negative scans had high-probability scintigrams, and two patients were found to have deep venous thromboses on lower-extremity sonography.

One patient died during follow-up, possibly because of recurrent pulmonary embolism, Dr. Braun said.

The negative predictive value of MDCT pulmonary angiography and venography was 96%, she added.

—Bruce K. Dixon

Cough, Fever, and Rash? Consider Coccidioidomycosis

BY SHERRY BOSCHERT
Elsevier Global Medical News

SCOTTSDALE, ARIZ. — Think of coccidioidomycosis in patients with a rash, fever, and cough, even if they don't live in the southwestern United States where *Coccidioides* is endemic.

At least two patients have presented to the Mayo Clinic, Rochester, Minn., with skin manifestations of coccidioidomycosis. Both patients were "snowbirds" who traveled to warmer climates in the southwest during the winter, according to physicians from the Mayo Clinic, Scottsdale, Ariz.

Although this mainly is a lung infection, cutaneous manifestations provide a clue to the diagnosis. "In the last 10 years at the Mayo Clinic in Arizona, I've been impressed by how often the dermatologist has a role to play in the diagnosis of coccidioidomycosis," Dr. David J. DiCaudo said at a dermatology conference sponsored by Skin Disease Education Foundation.

The desert areas of the southwestern United States and northern Mexico are the prime locations of this fungus, which is found in the western United States, Central America, and south to Argentina. Most U.S. infections occur in Arizona and in California's San Joaquin Valley, where a syndrome of the infection was first recognized and dubbed "valley fever," said Dr. DiCaudo of the Mayo Clinic, Scottsdale.

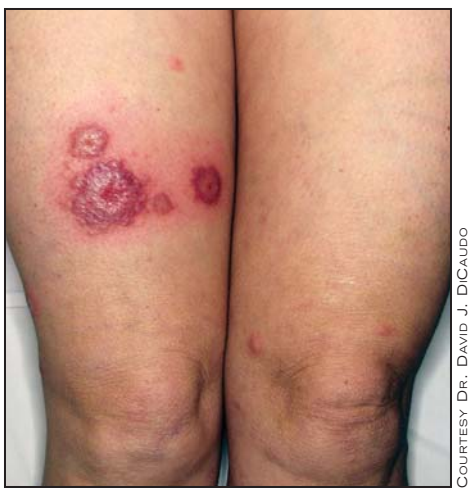
The incidence of coccidioidomycosis in Arizona more than tripled in the past decade, with a 56% increase in the past year alone. Droughts in recent years and construction activity stirring up soil and dust probably have contributed to the increase, he suggested. The organism lives in soil as filamentous mycelia that break down into arthroconidia, which can be carried on the wind and inhaled. Once inside people or animals, they transform into the spherule form recognized in biopsy specimens.

Most *Coccidioides* infections cause no symptoms. Around 40% of infected people develop a mild to moderate influenza-like illness with fever, cough, chills, and arthralgias. Even healthy people can be severely affected and laid low for weeks by the symptoms. Fewer than 1% develops severe infection or dissemination to the meninges or bones, with some deaths.

People of Filipino heritage are hundreds of times more likely to develop severe infection or dissemination, compared with the general population, and African Americans are at increased risk as well, Dr. DiCaudo said. People with compromised immune systems caused by pregnancy, HIV infection, organ transplant, or those using steroids or other immunocompromising medications also face greater risk with this infection.

The painful red nodules of erythema nodosum are the most common cutaneous manifestation of coccidioidomycosis. They typically appear on the lower extremities 1-3 weeks after the onset of systemic symptoms and suggest a good prognosis.

Other cutaneous symptoms appear earlier. Acute exanthem may appear in the first 24-48 hours of illness. "I've seen several patients who had a florid eruption even before the onset of any other symptom. Days later, they developed fever and cough," he said. The acute exanthem can resemble a drug reaction. Associated pruritus may be mild to severe. Lesions on the palms are common. It may last days or weeks.



COURTESY DR. DAVID J. DICAUDO

Sweet's syndrome is associated with pulmonary coccidioidomycosis.

The infection also can cause Sweet's syndrome, presenting as painful plaques, often but not always on the upper body, associated with fever and peripheral blood leukocytosis. In other settings, Sweet's syndrome commonly is treated with systemic steroids. "It's worth checking to make sure the patient doesn't have coccidioidomycosis first," because an immunosuppressant would increase their risk, Dr. DiCaudo said.

Granulomatous dermatitis can develop early in the course of the disease with widely distributed papules and plaques.

All of these cutaneous symptoms are reactive conditions; no *Coccidioides* will be found in the skin. The cutaneous symptoms evolve over a period of weeks or months as the patient recovers from the pulmonary infection.

A skin biopsy can be helpful, however, in rare disseminated infection, which typically develops 1-3 months after the onset of illness and can cause nodules, granulomatous plaques, and ulcers on the skin. It can mimic many other diseases including tuberculosis or acne. Even rarer is primary cutaneous infection at the site of inoculation, typically from injury by a laboratory pipette, a splinter, or even a cactus spine.

Serology is the key to diagnosing coccidioidomycosis. Keep in mind that the rash precedes seroconversion, so you may want to retest some patients with negative serologies 2 weeks later, he said. Low titers are common and shouldn't be dismissed.

The IgG antibody test can be positive and the IgM negative during active infection and shouldn't be interpreted as a past infection, he added. The antibodies tend to disappear following recovery, so a positive titer most likely represents acute infection.

The large spherules (10-80 mcm) of *Coccidioides* are easily seen under microscopy, typically as granulomatous or suppurative infiltrate. If needed, an in situ hybridization assay is available to distinguish the organism from *Blastomyces* or *Cryptococcus*.

Patients with coccidioidomycosis generally are managed by primary care physicians or infectious disease specialists.

Skin Disease Education Foundation and this news organization are wholly owned subsidiaries of Elsevier. ■

Plenty of Work Remains in Flu Pandemic Preparation

BY DAMIAN McNAMARA
Elsevier Global Medical News

Despite promising advances, clinicians, hospitals, and public health officials remain largely unprepared for a global influenza pandemic similar to the one in 1918 that killed more than 50 million people worldwide, according to an expert panel that held a Feb. 1 teleconference during the Seasonal & Pandemic Influenza 2007 meeting.

Primary care physicians on the front line of diagnosis and initial response need a better appreciation of the current morbidity and mortality caused by seasonal influenza outbreaks in the United States, Dr. Richard Whitley said.

In the event that an influenza pandemic occurred, it might incite more fear among physicians and the public, but seasonal influenza is known to cause an estimated 36,000 deaths and more than 200,000 hospitalizations each year, said Dr. Whitley, professor of pediatrics at the University of Alabama at Birmingham.

The American Academy of Pediatrics (AAP) and the American Academy of Family Physicians need to stress the importance of influenza vaccinations for members and the patients they treat, Dr. Whitley said.

"This message has been ignored for many years," he said.

"We need to immunize more children," as they are a main source of infection for other family members, including high-risk groups such as the elderly population and the immunocompromised. There have already been 100 children admitted to Children's Hospital in Birmingham and nine deaths so far in the United States during the 2006-2007 influenza season," Dr. Whitley said.

"So we've well exceeded acceptable levels of morbidity and mortality," he noted. "I would add that [the need for receiving immunization] applies to physicians who take care of adults as well," said Dr. John Bartlett, who is a professor of medicine at Johns Hopkins University, Baltimore.

"Data indicate the current vaccination [rate] is good in elderly, less so in the immunocompromised patients, and poor in health care workers, about 40%." It is clear that clinicians have a duty to protect themselves and their patients from influenza, he said.

One proposal for boosting vaccination rates among hospital-based health care providers is to make mandatory the reporting of such rates to the Joint Commission on Accreditation of Healthcare Organizations.

In addition, the Infectious Diseases Society of America (IDSA) is reportedly going to push for immunization of all health care workers.

"We've made some substantial advances, but we have a long way to go," said Dr. Anthony Fauci, director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Bethesda, Md.

One goal on the horizon that would help increase the number of people who are immunized is to reduce the prohibitively high doses of influenza vaccine that would be required during a pandemic, he said.

A quick point-of-care test for pandemic strains of influenza is in development, according to panel members.

A similar test for seasonal influenza strains, however, is limited by its long turnaround time.

"We need to get point of care diagnostics down to a time frame that is clinically useful. Now it takes several hours to do," Dr. Bartlett said. Having more rapid diagnostic assays would allow for more judicial use of antibiotics, particularly in children.

Panel members focused on the prevention of a bird flu pandemic caused by the H5N1 lethal strain of influenza virus subtype that mainly infects birds.

Worldwide as of Jan. 30, there were 270 confirmed human H5N1 cases, and 164 human deaths had been reported.

The vast majority of humans who have been infected by the H5N1 viral strain were in close contact with infected poultry.

"The greatest concern … is the resurgence of these viruses in countries such as Japan and Korea. … It suggests that migratory birds have probably brought these viruses back in," said Robert Webster, Ph.D., professor of virology at St. Jude Children's Hospital in Memphis, Tenn., and director of the World Health Organization's Center on Studies on the Ecology of Influenza in Animals and Birds.

The current resurgence following aggressive eradication efforts raises the question of what is the ultimate reservoir, said Dr. Webster. Until the reservoir is identified, "we cannot control it [H5N1]. … These viruses are diversifying at an amazing rate."

If a pandemic similar to the 1918 pandemic were to occur today, it would cause an estimated 62 million deaths worldwide (Lancet 2006;369:2211-8).

Health care resources in the United States would be quickly overwhelmed, according to data provided by the Center for Biosecurity at the University of Pittsburgh.

Researchers also estimated that an influenza pandemic similar to 1918 would take 191% of the beds in the United States.

Response to an influenza pandemic should be tailored to the extent of the outbreak—whether it is widespread as in 1918 or more mild, as in 1968, experts said.

'THE CURRENT VACCINATION [RATE] IS GOOD IN ELDERLY, LESS SO IN THE IMMUNOCOMPROMISED PATIENTS, AND POOR IN HEALTH CARE WORKERS, ABOUT 40%.'

The Centers for Disease Control and Prevention is releasing a strategy to categorize pandemic outbreaks on a 1 to 5 severity scale, similar to the scale currently used to rate the intensity of hurricanes.

"The distinction between a category 4 or 5 and a smaller pandemic is key," said Dr. Arnold Monto, a researcher at the University of Michigan School of Public Health in Ann Arbor.

"What we can take away from the 1918 pandemic in terms of school closings and social distancing—which occasionally occur if there is a big seasonal outbreak—is that they usually occur late after the outbreak has taken off," he said.

"It could be catastrophic if these measures are not taken in advance," Dr. Monto added.

The CDC initiative will address the utility of many of these nonpharmacologic means for control of a future influenza pandemic.

The Seasonal & Pandemic Influenza 2007 meeting was endorsed by the AAP, IDSA, CDC, NIAID, and by the Society for Healthcare Epidemiology of America. ■

Face Mask Allergy Followed SARS Outbreak in Toronto

BY HEIDI SPLETE
Elsevier Global Medical News

WASHINGTON — Cases of facial dermatitis in the wake of the severe acute respiratory syndrome outbreak in Canada in 2003 were traced to an allergy to formaldehyde from protective face masks, Dr. Jeffrey Donovan said at the annual meeting of the American Contact Dermatitis Society.

"A significant number of people presented at our contact dermatitis clinic with concerns about N95 mask allergies," said Dr. Donovan, a dermatology resident at the University of Toronto.

Results from a small study showed that prolonged use of the N95 masks had caused the masks to degrade and release formaldehyde, which was confirmed as an allergen in two allergic contact dermatitis cases. In addition, formaldehyde was a likely suspect in several cases of irritant contact dermatitis, Dr. Donovan said.

Severe acute respiratory syndrome (SARS) was identified in Toronto in 2003 in a woman who returned from a trip to Hong Kong and subsequently died from the illness. More than 400 cases of SARS were treated in Toronto hospitals, and strict protocols were enforced to prevent the spread of infection.

SARS transmission occurs primarily from person to person in the form of respiratory droplets, and the N95 protective face masks were recommended for any health care workers caring for patients with confirmed or suspected SARS.

The N95 masks are not new to health care workers, Dr. Donovan said. The typical protective face N95 mask is made of a combination of polyethylene and polypropylene, with a latex-free strap to secure it around the head and a polyurethane foam cushion at the bridge of the nose.

"However, instead of wearing them for short periods of time, as [may have been] done in the past, these masks were being worn constantly, for up to 12 hours at a time," he said.

In intensive care settings, health care workers wore goggles, face shields, and double gowns and gloves in addition to the masks. That fostered hot and humid conditions in the protective gear.

Dr. Donovan and his colleagues reviewed data from 13 health care workers (mean age 44 years) who presented to a clinic with contact dermatitis after wearing the N95 protective face masks for periods of several hours at a time. The patients had worked an average of 17 years in health care settings, and none had reported a previous reaction to an N95 mask.

TRACE AMOUNTS OF FORMALDEHYDE COULD BE RELEASED FROM THE MASK IF THE POLYPROPYLENE GOT TOO HOT AND BROKE DOWN.

Of these, eight patients were tested for reactions to the materials in the mask and to the North American Contact Dermatitis Group patch test series, but these tests were negative.

Two patients had widespread rashes on the trunk, neck, and thighs, as well as on the face. The investigators suspected an allergic reaction in these patients and an irritant reaction in the other six patients. The two patients who presented with a widespread rash had positive allergic reactions to a formaldehyde mix that is a commonly used screening agent for textile sensitivity.

The investigators evaluated a mask and confirmed the presence of formaldehyde, Dr. Donovan said. The mask manufacturer acknowledged that trace amounts of formaldehyde could be released from the mask in situations where the polypropylene got too hot and broke down.

The excess heat and humidity and unusual hospital conditions associated with the SARS outbreak may have released the formaldehyde from the face mask that caused the allergic reaction, explained Dr. Donovan. "Our recommendation is that masks be made from agents that won't degrade to formaldehyde, such as polyesters," he said. More studies are needed to investigate alternative materials that would not cause irritant or allergic reactions. ■

Dr. Susan Harding, FCCP, comments: *As with latex, many health care workers become sensitized to formaldehyde through experiences in school, research, pathology, or, as this report notes, wearing N95 face masks for prolonged periods of time. For now, health care workers should be made aware of this possibility when another respiratory infectious/biological epidemic occurs.*

Ventilator-Associated Pneumonia Haunts Neurologic ICU

Studies show that putting neurocritical care patients on a ventilator raises the risk of infectious fever.

BY KERRI WACHTER
Elsevier Global Medical News

BALTIMORE — Patients in the neurocritical care unit present a number of management challenges, but neurologists may be overlooking fever and infection, said one expert at the annual neurocritical care and stroke conference sponsored by Cleveland Clinic.

"I think that with all the focus neurologic staff have on the brain, we're ignoring the 800-pound gorilla …nosocomial infections," said Dr. Stephan Mayer, director of the neurologic intensive care unit at Columbia University Medical Center, New York.

Several studies have reported that 25%-50% of patients in the neurologic ICU have a temperature greater than 101° F. At the Columbia NICU, the fever rate is about 25%. When Dr. Mayer and his colleagues looked at these patients, they found two risk factors for development of fever in the NICU—longer length of stay and coma.

When they controlled for length of stay and coma, the researchers found that being on a ventilator significantly added to the risk of developing infectious fever. In fact, bronchopneumonia was the most common infection in the NICU—accounting for 60% of infections. The greatest risk factor for central (or unexplained) fever was ventriculostomy for intraventricular blood.

When an NICU patient develops a fever, the temptation is to go through the routine of getting a pan culture, chest x-ray, and lumbar puncture. But getting a thorough history, doing a thorough physical exam, and reviewing medications remain keys to identifying the infection, Dr. Mayer said. Noninfectious fever, for example, is often drug related.

Other causes of noninfectious fever include deep vein thrombosis/pulmonary embolism, chemical meningitis, transfusion reactions, surgical wound inflammation, cholecystitis, and gout. Subarachnoid hemorrhage increases the risk for both infectious and noninfectious fever.

Ventilator-associated pneumonia (VAP) is particularly common and very dangerous in the NICU. "Ventilator-associated pneumonias cause 10 times [more] morbidity and mortality than bloodstream infections," said Dr. Mayer.

"It would appear that neurologic patients have by far the highest rates of ventilator-associated pneumonia of any other type of critical care patient," said Dr. Mayer.

BRONCHOPNEUMONIA IS THE MOST COMMON INFECTION IN THE NEUROLOGIC INTENSIVE CARE UNIT, ACCOUNTING FOR 60% OF INFECTIONS.

Studies report that between 9% and 27% of patients ventilated for more than 48 hours develop VAP. The crude risk of VAP is 3% per day for the first 5 days, 2% per day for the next 5 days, and 1% per day thereafter.

"The take-home message is that when you decide to intubate someone for airway protection, you need to understand that there is a price that you pay with intubation. So if it's a sketchy indication, you need to balance this risk of infection against what you think are going to be the benefits of airway protection," Dr. Mayer said.

It's estimated that VAP adds an additional week to length of stay, raises the cost by about $40,000, and doubles the risk of mortality. "This is a very serious illness," Dr. Mayer said.

In 2005, the American Thoracic Society published guidelines on the management of VAP in adults (Am. J. Resp. Crit. Care Med. 2005;171:388-416). These guidelines focus on prevention, using aggressive empiric therapy, avoiding unnecessary antibiotic use, and the importance of recognizing local bacterial susceptibility patterns.

Prevention relies on the bundling of a number of techniques to minimize the risk of infection. The patient's head should be elevated to a 45-degree angle. NICU personnel should use alcohol hand disinfectants, gowns, and gloves. Patients should be extubated as soon as possible by using daily interruptions of sedation for minimal-assistance spontaneous breathing trials. Restrictive blood transfusion policies should be in place.

In addition, Dr. Mayer recommended using small-bore, postpyloric duotubes for patient feeding to avoid aspiration events. Make sure the endotracheal tube cuff pressure is adequate. Consider continuous aspiration of subglottic secretions. Oral antiseptics can also be used.

Clinical diagnosis relies on a chest x-ray with evidence of new infiltrates and two of the following symptoms: fever, purulent secretions, or leukocytosis. The sensitivity of these criteria is very high but the specificity is very low, noted Dr. Mayer. This can lead to unnecessary antibiotic use.

Definitive diagnosis relies on invasive lower respiratory tract culture. This means doing a bronchoscopy or bronchoalveolar lavage, or a collecting a protected brush specimen from down where the infection actually is.

"For this to work, your laboratory has to run quantitative bacterial cultures," said Dr. Mayer. Colonization greater than 10^4 or 10^5 colony-forming units/mL confirms infection.

"In a neurologic patient, if you have a fever you maybe have only a 40% or 50% likelihood tops that you're actually infected," said Dr. Mayer. "We are treating a lot of central fever in our unit with 8 days of double or triple antibiotics." Unnecessary antibiotic use is a big reason for problems with multidrug-resistant bacteria. "We need to be much more stingy with the antibiotics."

The treatment strategy depends on the timing of the pneumonia. VAP is divided into early (0-3 days) and late (4 days and beyond). Early VAP is usually less severe and much more likely to be due to gram-positive infections. Early VAP treatment should cover *Staphylococcus aureus, Haemophilus influenzae,* and *Streptococcus pneumoniae*. Late VAP is typically more severe and is much more likely to involve highly resistant gram-negative bacteria. Recommended treatment includes ampicillin/sulbactam, fluoroquinolones, or ceftriaxone or an equivalent third-generation cephalosporin.

Late VAP "is where you've got to cover for these multidrug-resistant gram-negatives," said Dr. Mayer. In particular, watch out for *Pseudomonas aeruginosa,* methicillin-resistant *S. aureus,* and vancomycin-resistant *Enterococcus.* Triple antibiotic coverage is recommended. Dr. Mayer recommends using vancomycin, piperacillin/tazobactam (or ceftriaxone or a carbapenem), and an aminoglycoside. Treat for the first 5 days or until laboratory results rule out highly resistant strains.

Focus antibiotic therapy on culture results once these are available. If culture reveals no infection, stop antibiotic therapy. "There's no difference in outcome if you treat for 8 days rather than 14 days," said Dr. Mayer. The exception is if the patient is not doing well clinically or if *Pseudomonas* is involved. ■

FDA Initiates Stricter Standards for Medical Glove Manufacture

BY ALICIA AULT
Elsevier Global Medical News

The Food and Drug Administration has issued a final rule that would require medical glove makers to improve their products' ability to serve as a barrier against pathogens.

Manufacturers are being given 2 years to comply with the new regulations.

The goal of the regulations is to reduce the risk of transmission of bloodborne pathogens such as human immunodeficiency virus (HIV) and hepatitis B, according to the Food and Drug Administration.

While the agency can't quantify how many cases might be prevented with better barriers, it estimated that approximately 2.4 HIV infections of U.S. health care workers occur each year because of "problems with the barrier protection properties of gloves used in healthcare settings."

The Food and Drug Administration estimates that 140 health care workers are infected with the hepatitis B virus on the job each year. These infections are primarily from percutaneous injuries. Approximately a third, or 40 cases per year, may be due to glove defects, according to the agency.

There is less evidence of an association between glove defects and hepatitis C infection, said the agency, noting that most occupational exposures are the result of needle sticks.

The agency has inspected medical gloves—used for patient examinations and surgical procedures—since 1990. At that time, the International Organization for Standardization (ISO), ASTM International, and the Food and Drug Administration had the same standards for glove quality. A few years later, the ISO and ASTM began requiring higher standards.

IF QUALITY STANDARDS WERE LEFT AT THEIR CURRENT LEVEL, 10 YEARS FROM NOW, SOME 1.2 BILLION DEFECTIVE GLOVES WOULD BE SOLD.

The Food and Drug Administration has allowed a defect rate of 4% for gloves used during patient exams and 2.5% for gloves used in surgery.

With more and more brands of gloves entering the medical marketplace and being sold, the agency hopes to maintain that defect rate. To do so means increasing the quality standards for glove manufacture, said the agency.

The Food and Drug Administration estimates that about 2% of the 39.2 billion gloves that are currently marketed are defective—or approximately 940 million gloves.

There are more than 400 manufacturers, but the number of medical gloves made and sold is expected to vastly increase during the next 10 years.

If quality standards were left at their current level, 10 years from now, some 1.2 billion defective gloves would be sold.

The agency said the benefits of higher standards for medical glove manufacture will outweigh the costs. It will cost about $6.6 million a year, but will result in savings of about $15 million due to less need for blood screens and a reduction in the number of infected health care workers.

The Food and Drug Administration first proposed increasing the standards for medical glove manuafacture in 2003.

The agency said it would fail lots that had visual defects—which brought complaints from glove makers that those defects may not necessarily mean the gloves are not effective.

But the agency said it will continue to fail lots that have either pinhole or visual defects, according to the final rule. ■

Tailor Empiric Antibiotic Therapy for ICU Trauma Patients

A successful strategy at Wake Forest uses pathogen colonization to determine drug choice and timing.

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT MYERS, FLA. — Proper choice of initial empiric therapy, timely testing for nosocomial infection, and selective antibiotic use are key treatment strategies for ventilator-associated pneumonia in trauma patients, according to a presentation at the annual meeting of the Eastern Association for the Surgery of Trauma.

"Getting [empiric therapy] right on the front end is associated with lower mortality," said Dr. Preston Miller III. Some clinicians question whether people are dying with or from ventilator-associated pneumonia (VAP), he said.

Researchers in one study found VAP to be an independent risk factor for death, with an odds ratio of 4.5 (Surg. Infect. [Larchmt] 2004;5:237-42). Another study outlined choices for empiric therapy in patients at high risk of nosocomial infection (Am. J. Resp. Crit. Care Med. 2005;171:388-416).

"Some of these [therapies] may or may not be necessary, depending on where you practice," said Dr. Miller of Wake Forest University, Winston-Salem, N.C.

The likelihood of nosocomial infection guides antibiotic selection, Dr. Miller said. He recommended taking a culture for nosocomial pathogens 7 or more days after admission. Using this 7-day timing is a strategy that worked well at Wake Forest, according to the study results he presented at the meeting.

Although 10-14 days of antibiotic treatment is commonly prescribed for VAP patients, "that is pulled out of a hat—there are no data to support that," Dr. Miller said at the meeting, which was jointly sponsored by Wake Forest University.

Antibiotic "de-escalation"—tapering or stopping antibiotic therapy when culture results are negative—is a practice that is gaining momentum. "It's hard to do. But there is more and more interest in shorter duration of therapy," said Dr. Miller, adding that increasing evidence supports the theory that shorter therapy does not necessarily increase resistance or mortality (Curr. Opin. Crit. Care 2006;12:452-7).

Dr. Miller and his associates conducted a two-phase study of VAP patients at Wake Forest. In phase 1, they looked at the timing of emergence of nosocomial infections among 110 patients. They found that at day 7 or 8, nosocomial pathogen colonization "starts to skyrocket" (J. Trauma 2006;60:725-29). "Indeed, those cultured on day 7 or later would have a much higher chance of nosocomial pathogen infection," he said. Therefore, "day 5 may not be the optimal day to expand coverage."

Investigators tested an antibiotic treatment algorithm based on cultures from 186 patients in phase 2 of the study. Ampicillin/sulbactam or moxifloxacin given to patients cultured before day 7 or cefepime or ciprofloxacin given to those demonstrating nosocomial infection at day 7 or later "works well at our institution," said Dr. Miller.

Use of the algorithm was supported by a higher overall accuracy of empiric therapy in phase 2 (83%), compared with phase 1 (74%). In addition, there was a trend toward significant improvements in mortality (13% in phase 2 vs. 21% in phase 1).

Antibiotic therapy to combat resistant gram-positive organisms is used at Wake Forest only for patients who are colonized or have had a previous VAP episode, Dr. Miller said. "We have a very low rate in our ICU—so we would end up overprescribing vancomycin otherwise."

There are no data to suggest that addition of a fluoroquinolone is associated with improved outcome in trauma ICU patients, Dr. Miller said. "I'm not saying it's bad. It's in the logical realm of medicine, but not the data realm." He added that the utility of this protocol probably needs to be based on the institution's bactogram.

"We do not use a fluoroquinolone unless we are up against the wall," Dr. Kimberly Davis, section chief, Trauma, Surgical Critical Care and Surgical Emergencies at Yale University, New Haven, Conn., said during the same panel presentation.

Tailoring therapy based on the prevalence of nosocomial pathogens at a particular institution is recommended by the American Thoracic Society guidelines for VAP after trauma (Curr. Opin. Crit. Care 2006;12:444-5).

Risk factors for nosocomial pathogen infection include hospitalization for more than 4 days, antimicrobial therapy in the preceding 90 days, long-term dialysis, home wound care, and a family member with a multidrug-resistant pathogen. Dr. Miller said he would add to this list people with chronic conditions who are in and out of medical facilities. ■

Severity Key in Initiating Therapy

Asthma • *from page 1*

is highly data driven, Dr. Nelson explained, and is based on 1,600 published articles culled from a total of 15,000.

While the existing guidelines emphasize asthma severity—mild, intermediate, and severe—the panel expanded the key elements of assessment and monitoring to include the separate but related concepts of control and responsiveness to treatment.

The draft guidelines emphasize asthma severity when initiating therapy but then shift the emphasis to asthma control when monitoring and adjusting therapy.

"Control is clearly the buzzword now," Dr. Nelson said in an interview. "Control is very well defined, and the guidelines explain what to do if control is not established."

The proposed guidelines also place greater emphasis on the two aspects of the asthma action plan: daily management, and early recognition of and actions for handling exacerbations.

"This change addresses confusion over the previous guidelines' use of different terms for asthma management plans. One term is now used," the panel wrote.

In pediatric asthma, the biggest proposed change involves separate recommendations for managing asthma in children younger than 5 years old and in those who are 5-11 years old.

'CONTROL IS CLEARLY THE BUZZWORD NOW. ... THE GUIDELINES EXPLAIN WHAT TO DO IF CONTROL IS NOT ESTABLISHED.'

"Treatment decisions for *initiating* long-term control therapy are based on classifying severity (considering both the impairment and risk domains) and selecting a corresponding step for treatment," according to the guidelines panel.

"The age 5-11 severity classification should guide initial therapy decisions, and inhaled steroids are still considered the preferred initial long-term controller," panel member Dr. Stanley J. Szefler said at the meeting, sponsored by the National Jewish Medical and Research Center.

As with adolescents (ages 12 years and older) and adults, asthma control assessment should then guide therapy adjustments, said Dr. Szefler, professor of pediatrics and pharmacology at the National Jewish Medical and Research Center.

"Impairment really tells you what's going on, and risk makes you think about what you should be considering in terms of … risk for exacerbations, progressive loss of lung function, reduced lung growth, or risk of adverse effects from medication," he said.

For children younger than 5 years, criteria for the initiation of long-term control of therapy are very important, and it's strongly recommended that these younger children be given pulmonary function tests. "Three-year-old children are able to undergo spirometry," Dr. Szefler said, adding that physicians are strongly urged to pay close attention to each child's medication step-down process.

Also new to the guidelines is information on vocal cord dysfunction and cough variant asthma as an alternative diagnosis.

The report is posted on the Web at www.nhlbi.nih.gov/guidelines/asthma/epr3. The public comment period ended March 5. ■

Dr. Susan Harding, FCCP, comments: *The ERR-3 draft report is now available for review on the Web. This draft is comprehensive and includes information on asthma definition, pathophysiology, pathogenesis, and natural history of asthma. More than 500 pages are dedicated to asthma management. This draft document is carefully indexed, so you can quickly review management strategies pertinent to specific situations. As noted, this is a draft that has been placed on the Web for public review and comment. It still requires approval.*

Fluticasone Monotherapy Best in PACT Asthma Study

BY LESLIE SABBAGH
Elsevier Global Medical News

Inhaled fluticasone monotherapy topped both inhaled fluticasone/salmeterol combination therapy and oral montelukast monotherapy in the treatment of children with mild to moderate persistent asthma, according to a randomized, double-blind clinical trial.

Dr. Loren C. Denlinger of the University of Wisconsin, Madison, and colleagues summarized results from several guideline-defining asthma clinical trials, including the Pediatric Asthma Controller Trial (PACT).

The PACT study, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), compared the safety and efficacy of three asthma medicines for first-line therapy in children aged 6-14 years with mild to moderate persistent asthma (J. Allergy Clin. Immunol. 2007;199:64-72).

The children enrolled in a run-in period of 2-4 weeks, during which they received a placebo Diskus twice daily, an evening placebo capsule, and an albuterol MDI for rescue therapy.

Of 648 participants screened, 285 were randomized to one of three double-blind, 48-week regimens: inhaled fluticasone 100 mcg in the morning and 100 mcg in the evening; the PACT combination of inhaled fluticasone 100 mcg and salmeterol 50 mcg in the morning (Advair Diskus) and inhaled salmeterol 50 mcg in the evening (Serevent Diskus); or oral montelukast 5 mg (Singulair) in the evening.

At baseline, all children in the study had forced expiratory volume in 1 second (FEV_1) values of 80% predicted or better.

At 48 weeks, all three controller therapies resulted in improved asthma control days (ACDs). The fluticasone monotherapy group, however, gained an average of 42 ACDs per year compared with the montelukast-only group. The fluticasone monotherapy and the PACT combination groups had similar ACDs and asthma exacerbation prevention, but fluticasone alone had better clinic-measured FEV_1/FVC (forced vital capacity) maximum bronchodilator response and PC_{20} values. There were no significant adverse growth effects seen for any medicine studied.

The findings of the PACT study "favor fluticasone monotherapy because of its overall success in improving asthma control outcomes," the reviewers wrote. The study gives "definitive evidence in support of guideline recommendations of low-dose inhaled corticosteroids in treating children with mild to moderate persistent asthma."

"In this limited study, fluticasone monotherapy appears to be superior to PACT combo and montelukast in greater number of ACDs and pulmonary function," Dr. LeRoy M. Graham, FCCP, of Morehouse School of Medicine, Atlanta, said in an interview.

However, "the caution is to realize that studies give averages, and there are subpopulations who may not achieve the same results," he said.

Some of the study's authors consult or receive funding from Aventis, GlaxoSmithKline, Merck, AstraZeneca, Novartis, Bristol-Myers Squibb and Eli Lilly & Co. Dr. Denlinger has declared that he has no conflicts of interest. ■

Dr. Susan Harding, FCCP, comments: *These results are important, because the study focuses on three asthma controller regimens for first-line asthma therapy in school-aged children with mild-to-moderate persistent asthma. [Dr. Harding has no conflicts of interest with any of the companies that manufacture the medications used in this trial.]*

hMPV Common in Children With Alveolar Pneumonia

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO — Human metapneumovirus emerged as the second most common virus detected during a 4-year study of young children with alveolar pneumonia who were admitted to the emergency department, Dr. Dana G. Wolf reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The finding is important because while an association between human metapneumovirus (hMPV) and bronchiolitis has been documented, "the involvement of hMPV in pneumonia remains unknown," said Dr. Wolf, who is the head of clinical virology in the department of clinical microbiology and infectious diseases at the Hadassah University Hospital, Jerusalem.

hMPV WAS DETECTED IN 8.3% OF THE CHILDREN ADMITTED WITH ALVEOLAR PNEUMONIA, COMPARED WITH ONLY 2.2% OF THE CONTROLS.

Dr. Wolf and her associates prospectively obtained nasal wash specimens from 1,296 children aged 5 years or younger who were admitted to the hospital's emergency department with alveolar pneumonia and from 136 age-matched controls who were admitted for elective surgery between November 2001 and October 2005.

The researchers used two methods of identifying viral pathogens: real-time polymerase chain reaction (PCR) to test for the presence of hMPV, and direct immunofluorescence or real-time PCR to test for respiratory syncytial virus (RSV), adenovirus parainfluenza, and influenza viruses.

Dr. Wolf reported that of the children tested, hMPV was detected in 108 (8.3%) of the children admitted with alveolar pneumonia, compared with only 3 (2.2%) of the controls. hMPV was the second most common viral pathogen after RSV (23.1%), followed by adenovirus (3.4%), parainfluenza (2.9%), and influenza A (2.9%).

Most hMPV infections (88%) occurred during the period from November to May, and hMPV was the second most common virus detected in each of the 4 years.

Specifically, hMPV was detected between November and May in 14.5% of patients in year 1; 5.8% of patients in year 2; 6.2% of patients in year 3; and 12.2% of patients in year 4.

When the investigators analyzed the data, they found differences in the rates of RSV infection by age. Specifically, 37% of children who were younger than 1 year of age were infected with RSV, compared with 11% of those aged 1 year and older.

By contrast, the rates of hMPV infection remained the same among both age groups (6.5%).

"The important role of hMPV in community-acquired alveolar pneumonia, which is usually considered to be of bacterial origin, supports the notion of hMPV-bacterial coinfection as suggested by vaccine probe studies," Dr. Wolf said at the meeting, sponsored by the American Society for Microbiology. ■

Dr. LeRoy M. Graham, FCCP, comments: *hMPV is an important etiology of alveolar pneumonia in children and may be complicated with bacterial coinfection.*

CPAP Success Improved Survival in Heart Failure

BY KATE JOHNSON
Elsevier Global Medical News

MONTREAL — Suppression of central sleep apnea with continuous positive airway pressure is associated with increased survival among patients with heart failure, according to a subanalysis of the CANPAP trial.

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial showed that CPAP did not improve overall heart transplant–free survival (N. Engl. J. Med. 2005;353:2025-33), explained primary investigator Dr. T. Douglas Bradley at the Eighth World Congress on Sleep Apnea.

But when the CPAP-treated patients were analyzed according to whether or not their central sleep apnea was suppressed after 3 months of treatment—meaning that their apnea-hypopnea index (AHI) was reduced to a score below 15—the investigators found a benefit to CPAP in terms of improved left ventricular ejection fraction and heart transplant–free survival.

The findings "suggest reduction of AHI is a sign of better cardiovascular outcome in such patients," said Dr. Bradley, director of the center for sleep medicine and circadian biology at the University of Toronto. "If you've got a heart failure patient with central apnea, you can safely have them on CPAP for a period of a month or so and then restudy them. But if their apnea-hypopnea index hasn't gone down at that point, you should probably stop the CPAP."

The CANPAP trial randomized 258 heart failure patients with central sleep apnea and optimal medical therapy to either CPAP (128 patients) or a control group (130 patients).

The study showed no difference in left ventricular ejection fraction or heart transplant–free survival between the two groups after a mean follow-up of 2 years. However, the trial was underpowered, said Dr. Bradley, probably because the addition of new drugs—such as β-blockers and spironolactone—during the study period was associated with an overall decline in heart failure deaths.

The subanalysis included only 200 patients who completed a follow-up assessment 3 months after randomization. Patients randomized to CPAP were divided into those whose central sleep apnea was suppressed to fewer than 15 events per hour of sleep (57 patients), or those in whom it was not (43 patients). Compared with controls, the suppressed patients had significantly improved survival (hazard ratio 0.37). In the control group, 12 patients had spontaneously suppressed, but this low number of patients was insufficient to determine whether spontaneous regression of central sleep apnea was associated with improved outcomes, noted Dr. Bradley.

"This is a secondary, unplanned, retrospective analysis, and so must be interpreted with caution," he said. "Nevertheless, the differences are striking. If patients' AHI was suppressed below 15, there was hardly any mortality—so it's something we can't ignore."

OSA Screening Is Important in Coronary Heart Disease

SALT LAKE CITY — The prevalence of obstructive sleep apnea in patients with coronary heart disease may be higher than previously thought, according to data presented at the annual meeting of the Associated Professional Sleep Societies.

In a study of 132 patients with a history of myocardial infarction or angiographically verified coronary artery disease, the prevalence of obstructive sleep apnea was 70%, Robert M. Carney, Ph.D., reported in a poster presentation.

Some previous studies have suggested prevalence rates in the 50% range in this population.

Patients in the current study underwent 2 nights of polysomnography. Obstructive sleep apnea was defined as at least five episodes of obstructive apnea or hypopnea per hour, noted Dr. Carney, professor of psychiatry and director of the Behavioral Medicine Center at Washington University, St. Louis.

The finding underscores the importance of screening heart disease patients for obstructive sleep apnea, which has been shown to increase the risk of myocardial infarction in this population, Dr. Carney concluded.

—Sharon Worcester

Seniors Not at Greater AF Risk

Atrial Fibrillation • *from page 1*

and the investigators reported it was a strong predictor (hazard ratio 2.18) of future atrial fibrillation. A total of 4.3% of patients with obstructive sleep apnea but only 2.1% without the disorder were subsequently diagnosed with atrial fibrillation.

An age-stratified analysis showed patients younger than 65 years were more vulnerable to atrial fibrillation, however, and had more risk factors. The most significant was lower oxygen levels at night (hazard ratio 3.29), but age (2.04), male gender (2.66), coronary artery disease (2.66), and body mass index (1.07) also were predictors. In older patients, heart failure had a hazard ratio of 7.68.

Why the older patients were less susceptible to atrial fibrillation is unclear, according to the authors. Dr. Somers, a professor of medicine at the Mayo Clinic, speculated that the older patients probably had undiagnosed apnea for many years.

"If you have sleep apnea and you last to 65-70 years without developing atrial fibrillation, you are going to be okay—you are going to be okay," he said. "But if you are susceptible to the damage that sleep apnea does to your cardiovascular system, you will develop atrial fibrillation earlier."

Dr. Somers emphasized that this was a retrospective study in a referral population, and that the findings needed to be confirmed by prospective investigation.

Dr. Somers is a consultant for Cardiac Concepts and is coinvestigator on a grant from the ResMed Foundation, which funded the study. The present study, for which the lead author was Dr. Apoor Gami, follows earlier research at the Mayo Clinic that showed an association between obstructive sleep apnea and atrial fibrillation.

In one study, Dr. Gami, Dr. Somers, and coinvestigators found obstructive sleep apnea was "strikingly more prevalent" (odds ratio 2.19) in atrial fibrillation patients than in general cardiology patients. About 49% of 151 patients who underwent electrocardioversion for atrial fibrillation had obstructive sleep apnea vs. about 32% of 312 patients treated for other heart conditions (Circulation 2004;110:364-7).

In a study of patients who underwent electrocardioversion, Dr. Somers' group found atrial fibrillation was more likely to recur if obstructive sleep apnea was not treated (Circulation 2003;107:2589-94). ■

The Evidence

Despite presenting strong evidence of an association between obstructive sleep apnea and cardiovascular disease, Dr. Somers was careful not to say that treating the sleep disorder would prevent heart disease.

"Beyond lowering blood pressure and perhaps increasing EF [ejection fraction] in people with heart failure, treating sleep apnea has not been proven to prevent any cardiovascular end points," he said.

"We have no evidence that treating sleep apnea will prevent a cardiac death, a heart attack, a stroke, or anything," he said. "All we have now are soft end points—blood pressure, [and] heart rate."

Many markers of heart disease—notably hypertension, elevated levels of C-reactive protein, and systemic inflammation—occur with sleep apnea, according to Dr. Somers. Consequently, he maintained, it makes sense that an untreated apnea could lead to cardiovascular disease.

In addition to his work showing a link with atrial fibrillation, he cited studies associating sleep disorders with hypertension, sudden cardiac death, and heart failure. Among these findings, he noted the following:

- Apnea can cause hypertension, and hypertension becomes worse if apnea is not treated (N. Engl. J. Med. 2000;342:1378-84).
- Obstructive sleep apnea patients were two to three times as likely to have a first-degree relative who died of a heart attack or suddenly of an unexplained cause, according to a review of 500 people by Dr. Somers and his colleagues (Chest 2007;131:118-21).
- While 6 a.m.-11 a.m. is the peak time for sudden cardiac deaths in the general population, 46% of sudden cardiac deaths in people with obstructive sleep apnea occurred between midnight and 6 a.m. (N. Engl. J. Med. 2005;352:1206-14).

About 10% of heart failure patients have obstructive sleep apnea and 40% have central sleep apnea, Dr. Somers added, attributing the data to studies conducted in the 1990s. Although Dr. Somers believes in treating sleep disorders to prevent heart disease, he added that his colleagues in cardiology won't be convinced until cause and effect is proved.

AMERICAN COLLEGE OF CHEST PHYSICIANS®

NEWS FROM THE COLLEGE

PRESIDENT'S REPORT

Planning for CHEST 2007

BY DR. MARK J. ROSEN, FCCP

The major mission of the ACCP is to provide outstanding education, and our members tell us that the two most important benefits of membership are a subscription to *CHEST* and attending our annual meeting.

Like all of our annual meetings, most attendees at CHEST 2007 will have access to an educational menu of the latest developments in pulmonary, critical care, sleep medicine, and cardiothoracic surgery, with an array of outstanding speakers and sessions arranged almost perfectly (*nothing* is perfect, but we try), all to help us help our patients. This meeting consistently runs so well that most think it would not be that hard to put together. However, the annual meeting is the result of a year-long complex process, requiring preparation, organization, and coordination of input from the ACCP NetWorks, the Continuing Education Committee, the general membership, our sister organizations, and the College leadership and staff.

As in previous years, the planning process for CHEST 2007 started during CHEST 2006, with the first meeting of the Program Committee, and continued through the final meeting at the ACCP offices in Northbrook in January 2007. Under the skillful and indefatigable leadership of Dr. Brian Carlin, FCCP, the Scientific Program Chair of CHEST 2007, and Dr. Suhail Raoof, FCCP, Chair of next year's meeting, a mélange of outstanding proposals from a wide variety of sources somehow got organized into a coherent schedule for a program that we can all look forward to attending. When talented people do something difficult, they make it look easy. Planning this meeting is definitely not easy, and the members should know how it is done. My purpose is not only to show how we work, but to encourage you to participate.

First, proposals for specific topics and speakers are submitted online either by the NetWork Steering Committees or by individual members. Most come through the NetWorks; each NetWork's Steering Committee selects topics, picks the ones that it believes are most important, and submits them online on a standardized format. Probably the most effective way to get your favorite topic, speakers, or yourself on the program is by participating actively in a NetWork that reflects your interests. Alternatively, anyone can submit a proposal for a session directly to the Program Committee by completing a standardized form on the ACCP Web site. All proposals must include a title, description, educational needs assessment, learning objectives, key word association (for sorting in the printed program), type of session (meet-the-professor, plenary, pro-con), speaker information, and "curriculum track" (pulmonary, sleep, pediatrics, etc). They then go into a database, where they are collected, sorted, and sent to the Executive Program Committee and the most relevant NetWork to be scored on another database.

WHEN TALENTED PEOPLE DO SOMETHING DIFFICULT, THEY MAKE IT LOOK EASY. PLANNING THIS MEETING IS DEFINITELY NOT EASY.

The Executive Program Committee includes the immediate past, present, and future Program Chairs and ACCP Presidents, Chairs of the NetWorks, the Continuing Education, Affiliates, and Health and Science Policy Committees, along with selected committee liaisons and ACCP leadership. In addition, there are representatives from our partners, the Canadian Thoracic Society and the American Association of Critical-Care Nurses.

All of the submissions are graded by the Program Committee and a relevant NetWork Steering Committee and the results tabulated and sorted. A program grid with time slots is designed in advance to accommodate a proportional representation of topics in pulmonary medicine, sleep, critical care, cardiovascular disease, thoracic surgery, and pediatrics. Some sessions are reserved for sister societies and others for the honor and memorial lectures. Then, at the Program Committee meeting, they are discussed, prioritized, and placed into a program grid, starting with the programs with the highest scores. The Committee also determines appropriate formats (such as panel, plenary) and modifies programs to correct for perceived bias, and conflicts of interest are noted.

During the Northbrook meeting, the Program Committee functioned like an orchestra, except they also had to compose the score from a few hundred random notes, chords, and phrases. Here, hundreds of submissions were culled down and shaped into a coherent program. Dr. Carlin was the conductor, a maestro of focus, organization, judgment, and taste, who literally did not sit down while the meetings were in session. All that was missing was the baton. Like the strings, winds, brass, and percussion, others were instrumental (bad pun, unintended, I apologize) in their own ways. Dr. Raoof chaired the committee to nominate the honor lecturers and worked continuously during the Program Committee to track the session assignments in relation to the predetermined distribution of topics. Drs. Lisa Moores, FCCP (Program Chair of CHEST 2009), Stephanie Levine, FCCP, Darcy Marciniuk, FCCP, and Michael Baumann, FCCP (past Program Chairs), provided continuous fact-checking, time-tracking, and sage counsel. Dr. Kevin Chan, FCCP, was stationed at the "Master Grid" (our final composition), doing magic with Velcro and little slips of paper for each session and making sure that gaffes like two COPD talks at the same time did not happen, or at least happened only if there was modest overlap and no alternative. And throughout, our virtuoso ACCP staff (Ed Dellert and his CHEST 2007 team) continuously displayed information on projected images, processed the Committee's decisions, tracked, sorted, edited, and just made beautiful music together.

The program can still change. Many times in prior years, we have successfully adjusted the program for late-breaking news and events.

I believe that CHEST 2007 will be outstanding, and I look forward to seeing you. ■

EDUCATION INSIGHTS

Quality Improvement Committee Debuts Web Site

BY SANDRA ZELMAN LEWIS, PHD;
ACCP Research Analyst
AND ED DELLERT, RN, MBA
Vice President, Educational Resources

The ACCP Quality Improvement Committee (QIC), now a 1-year-old, fully constituted standing committee of the ACCP since October 2006, invites all ACCP members to peruse and bookmark the new QI Web site. This site can be accessed under the Education tab on the menu bar of www.chestnet.org.

From the home page of the new QI Web site, you can download a podcast of the popular Keynote Address from CHEST 2006, "Quality Improvement, Performance Measures, and Pay for Performance: Why You Should Care." Bookmark this page so that you can periodically find announcements of new performance measures endorsed by the committee and available ACCP QI products.

As a new body, the QIC has defined its mission and developed processes and policies to guide its current major work in the review of performance measures and plans for the future. We anticipate providing implementable tools to help ACCP members with their local QI activities and their impact on clinical practice. The background and priorities of this committee, as well as the mission statement and roster of members, may be reviewed on the Web site. The policies and processes are clearly documented and algorithmically illustrated if you select the tab "Functions and Processes."

One of the most interesting items on the site is the list of actions taken by the committee since its inception 1 year ago. The responses to the measures set forth by the National Quality Forum and the AMA-Physicians Consortium for Performance Improvement are listed in a large pdf file that can be downloaded by selecting the "QIC Database of Actions" tab. This file documents all the formal votes and public comments that were submitted in response to the following sets of measures: VTE, asthma/respiratory care; palliative and hospice care; cardiology; pulmonary; serious reportable events; safe practices; end of life in cancer patients; stroke and stroke rehabilitation; and pneumonia mortality. The latest set of measures on substance abuse includes several on tobacco dependence screening and treatment, which meet QIC selection criteria; thus, these are also included. This list will be updated monthly.

Elsewhere on the QI Web site you will find a glossary of QI terms and acronyms, links to external organizations' Web sites, and a calendar of events that will keep you updated about important meetings and events pertaining to quality improvement.

Contact us with your questions and remarks directly from the Web, or send them to Sandra Zelman Lewis, PhD, at slewis@chestnet.org.

We hope that you find value in this new Web site, and we would appreciate receiving your ideas and comments. ■

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS®

We're in the News

BY JENNIFER STAWARZ
Senior Manager, ACCP Public Relations

The American College of Chest Physicians and The CHEST Foundation have maintained a strong presence in the news through the end of 2006 and into 2007. Media coverage for CHEST 2006 proved successful, generating more than 800 print, broadcast, and Internet stories related to scientific abstracts presented at the meeting. In addition to media coverage mentioned in March's issue of *CHEST Physician*, CHEST 2006 stories have since appeared in: *Orange County Herald; New York Daily News; Sydney Morning Herald; Baltimore Sun; Men's Health Magazine; Family Practice News;* and *Oncology Times.*

During the ACCP annual meeting, The CHEST Foundation honored 16 recipients of the 2006 Humanitarian Awards. Media outreach in the recipients local markets generated several print and Internet stories, including those seen in: *Beaumont Enterprise; Birmingham News; Winston-Salem Journal*; *Corpus Christi Caller-Times*; *Los Angeles Times* online; *Chicago Hospital News;* and *Advance for Managers of Respiratory Care.*

Following the annual meeting, press releases related to studies in *CHEST* received significant media interest.

In March, a study that showed Florida red tides can be harmful to people with asthma resulted in numerous placements, including the *New York Times,* the *Washington Post,* the *Miami Herald,* and more than 20 broadcast stations around the US.

Also in March, the CDC released a report stating that cough medicines should not be given to babies and toddlers. The Associated Press (AP) released a story highlighting the CDC report and included a mention of the ACCP cough guidelines, published in 2006. As a result of the AP story, the ACCP has been featured in more than 250 print, broadcast, and Internet media outlets.

Partnering for COPD Awareness

On March 18, the National Heart, Lung, and Blood Institute (NHLBI) launched its *Learn More Breath Better* campaign to raise public awareness about COPD.

As part of the launch, the NHLBI hosted a press conference in Washington, DC, that featured speakers from partnering societies, including ACCP President, Dr. Mark J. Rosen, FCCP.

See the February issue of *CHEST Physician* for details. ■

ACCP Live Interactive Web-Based Seminar

Do you know how to effectively incorporate the use of nonphysician providers in your practice?

By using nonphysician providers in your practice, you can:

- Increase profitability.
- Improve patient flow by allowing the physician to focus on more complex medical issues.
- Provide more free time for the physician to engage in other practice responsibilities.

The benefits of using nonphysician providers are only maximized if their use is effectively coordinated with the physician.

Learn how!

"Using Nonphysician Providers in Your Practice," an American College of Chest Physicians live interactive Web-based seminar, will be held Tuesday, April 24, 2007, at 12:30 PM – 2:00 PM EST.

(Registration for the seminar closes on April 23, 2007 at 6:00 PM EST.)

Registration cost is $250. You can register at www.chestnet.org.

If you would like more information about this live interactive Web-based seminar, please contact jbruno@chestnet.org. ■

call for abstracts

ABSTRACT SUBMISSION DEADLINE: MONDAY, APRIL 30, 2007

Be part of the CHEST 2007 program by submitting an abstract of your original investigative work for presentation during the meeting.

- **Gain international exposure.** Your work will be presented to an international audience and published in a *CHEST* supplement.
- **Receive feedback** from the clinicians likely to use your data in their practices. Health-care professionals in chest and critical care medicine will review and comment on your work.
- **Participate with the ACCP in efforts to fight chest diseases.** By presenting your findings, you join the ACCP in its mission to advance the prevention and treatment of chest diseases through research and education.
- **Compete for ACCP investigative awards.** Monetary awards are granted by The CHEST Foundation to investigators whose work is judged to be outstanding by the reviewers.

Abstract submission to CHEST 2007 is FREE. Domestic and international submissions are encouraged. Abstracts will be graded individually on scientific merit and originality. Abstract submission begins in February. Submit online at www.chestnet.org by clicking on the Abstracts and Case Reports Submission link when available. For questions, call (800) 343-2227 or (847) 498-1400.

Categories for submission include:

AIDS
Asthma
Bronchoscopy and Interventional Procedures
Cardiovascular Disease
Cardiovascular Surgery
COPD
Critical Care—ARDS/Lung Injury
Critical Care—Outcomes
Critical Care—Sepsis
Cystic Fibrosis
Cytokines/Cellular Interactions
Ethics
Geriatrics
Health Economics and Practice Administration
Home Care
Interstitial Lung Disease
Lower Respiratory Tract Infections
Lung Transplant and Immunology
Mechanical Ventilation: Management
Mechanical Ventilation: Weaning
Occupational/Environmental Lung Disease
Pediatric Chest Disease
Pleural Disease
Pulmonary Physiology/PFTs/Rehabilitation/Exercise
Pulmonary Vascular and Thromboembolic Disorders
Sleep
Smoking Cessation and Tobacco Control
Tele-Education
Thoracic Oncology: Diagnosis
Thoracic Oncology: Therapy
Thoracic Surgery
Tuberculosis
Women's Health

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AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

NetWorks: Consensus Statement; Leadership Development

Pediatric Chest Medicine

One year ago, the Pediatric Chest Medicine NetWork, in conjunction with the Home Care NetWork, convened a panel to produce the ACCP Consensus Statement on the Respiratory and Related Management of Patients with Duchenne Muscular Dystrophy Undergoing Anesthesia or Sedation. The panel consisted of specialists in the areas of anesthesiology, critical care medicine, neurology, orthopedic surgery, pediatric and adult pulmonology, and respiratory therapy. This statement is now in its final stages of development.

Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease transmitted by X-linked inheritance and occurring with an incidence of approximately one in 3,500 live male births. DMD affects the muscles of respiration and is associated with dilated cardiomyopathy, which often leads to death from cardiopulmonary causes.

A statement on this topic is needed for several reasons. First, patients with DMD are at risk of severe complications when they undergo sedation or anesthesia. Second, with contemporary cardiopulmonary management, including the widespread use of noninvasive positive pressure ventilation (NPPV), persons with DMD are experiencing an unprecedented duration of survival, and they are requiring surgical procedures with unprecedented frequency. The risks related to anesthesia and sedation for patients with DMD include potentially fatal reactions to inhalation anesthetics and certain muscle relaxants, upper airway obstruction, hypoventilation, atelectasis, congestive heart failure, cardiac dysrhythmias, respiratory failure, and difficulty weaning from mechanical ventilation.

The statement is divided into sections on the assessment and management of patients before, during, and after procedural sedation or general anesthesia. The panel used the limited scientific literature and consensus opinion, obtained by majority vote, to formulate advice regarding the highly interrelated areas of respiratory, cardiac, GI, and anesthetic management of patients with DMD when they require sedation or anesthesia.

The specific suggestions include advice on preoperative measurement of selected pulmonary function parameters, with identification of threshold levels that place patients at risk of respiratory complications, and suggestions for preoperative training of patients in the use of NPPV and assisted cough via mechanical insufflation-exsufflation (MI-E).

The statement includes advice on the optimal medical setting and personnel who should be in attendance when patients undergo sedation or anesthesia; how to choose safe anesthetic agents; suggestions for pre- and postoperative cardiac, nutritional, and GI management; and more.

The purposes of the statement are to aid clinicians involved in the care of patients with DMD undergoing procedures requiring sedation or general anesthesia; to be a resource for other stakeholders in this field, including patients and their families; for use as an up-to-date summary of medical literature on this topic; and to identify areas in need of future research.

For more information, contact networks@chestnet.org.

Private Practice

This year at CHEST 2007, private practice physicians will have the opportunity to participate, along with academic physicians, in a leadership development program.

The purpose of this 1-day conference is to introduce ACCP members to opportunities to work, in their particular areas of interest, within the leadership of the College.

It also provides an area to explore ethical, political, and clinical issues of importance to today's practicing physician. The format consists of both formal and informal discussions and presentations.

The Private Practice NetWork contributes to the content for the conference. Topics have included coding and reimbursement issues, the use of physician extenders in clinical practice, managing a multiple physician organization, and contract negotiations with prospective practice associates and hospitals.

This year's program will be held on October 20, 2007, in Chicago. Attendees will learn how to become active in leadership activities within the ACCP, as well as within their local practices and communities.

Contact Marla Brichta at mbrichta@chestnet.org. ■

New *CHEST* Benefits Now Available

CHEST Papers in Press

www.chestjournal.org

The American College of Chest Physicians (ACCP) now provides its readership with *CHEST* Papers in Press. In partnership with our online host, HighWire Press, we publish online—within weeks of their acceptance and months before print publication—peer-reviewed original research articles submitted to and accepted by *CHEST*.

According to Dr. Richard Irwin, FCCP, Editor in Chief of *CHEST*, "This initiative is another in a series of technological advances to improve the efficiency of the editorial process started by my predecessor, Dr. A. Jay Block. *CHEST* Papers in Press will dramatically reduce the time to publication, accomplishing a key goal of the ACCP and *CHEST*: providing authors, clinicians, and researchers around the globe with online subscription-based access to the latest clinical research."

CHEST Papers in Press are citable, searchable in PubMed, and will establish publication priority. These articles are published online in PDF format and represent the original accepted, unedited version of the manuscript as it was submitted by the author. These articles will bear a citable digital object identifier (DOI) number.

After a paper is published online through *CHEST* Papers in Press, it continues through the normal production and copy editing processes that lead to its publication in print and the final online editions of *CHEST*. The final versions will identify the year, volume, issue, and page numbers, as well as the Papers in Press DOI.

The final versions will appear in print and online and be accessible through database and PubMed searches, while the original Papers in Press version will be stored in a permanent accessible archive.

The ACCP and *CHEST* hope that this important service to our authors and readers will continue to underscore our goals of providing fast access to the most recent clinical research in our fields. View *CHEST* Papers in Press on the journal home page, www.chestjournal.org

CHEST Archive

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The ACCP and *CHEST* are proud to announce the launch of the *CHEST* Archive—online back issues of *CHEST* from Volume 12, Number 1 (January 1946), available in a permanent, accessible, searchable online archive.

And to underscore our commitment to the access of information, we are making this archive FREE to view.

CHEST currently makes all content free 1 year after publication, and we have extended this policy to the *CHEST* Archive's content back to 1946.

The *CHEST* Archive can be searched and freely accessed in PDF scanned images of printed pages.

For more information about *CHEST* online and the *CHEST* Archive, go to www.chestjournal.org.

To subscribe to *CHEST*, you can contact ACCP Customer Service at www.chestnet.org. ■

**Back issues from January 1999 to the present are part of CHEST's ongoing online program and are made available for free to the public 12 months after publication.*

This Month in *CHEST*: Editor's Picks

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

- **Registering a Clinical Trial in Clinical Trials.gov.** *By Dr. D. A. Zarin; and Dr. A. Keselman*
- **Sildenafil Improves Walk Distance in Idiopathic Pulmonary Fibrosis.** *By Dr. H. R. Collard, FCCP, et al*
- **Significance of Pulmonary Arterial Pressure and Diffusion Capacity of the Lung as Prognosticator in Patients With IPF.** *By Dr. K. Hamada, et al*
- **Pulmonary Hypertension and Pulmonary Function Testing in Idiopathic Pulmonary Fibrosis.** *By Dr. S. D. Nathan, FCCP, et al*
- **Lung CT Densitometry in Systemic Sclerosis: Correlation With Lung Function, Exercise Testing, and Quality of Life.** *By Dr. G. Camiciottoli, et al*
- **Respiratory Bronchiolitis-Interstitial Lung Disease: Long-term Outcome.** *By Dr. J. Portnoy, FCCP, et al*
- **Inspiratory Muscle Unloading by Neurally Adjusted Ventilatory Assist During Maximal Inspiratory Efforts in Healthy Subjects.** *By Dr. C. Sinderby, et al*
- **A Pooled Analysis of FEV_1 Decline in COPD Patients Randomized to Inhaled Corticosteroids or Placebo.** *By Dr. J. B. Soriano, et al*

www.chestjournal.org

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

SLEEP STRATEGIES

Sleep Medicine Education: Past, Present, and Future

Education efforts are crucial to improving the overall care of patients with sleep disorders.

Sleep Strategies begins its second year as a bimonthly column in *CHEST Physician*.

I thank Dr. Susan Harding, FCCP, our editor in chief, for doing such an outstanding job in getting *CHEST Physician* off to a successful start. I also want the readers to know of the great behind-the-scenes work of Pam Goorsky, ACCP Assistant VP of Editorial Resources, who keeps the publishing train on track.

Thank you Sue and Pam!

With the start of the new year, I thought it appropriate to review sleep medicine education in the College, with a focus on last year and what will be coming up this year.

This is particularly timely and important as many College members study for the new American Board of Internal Medicine board examination in sleep medicine, to be first given in mid-November of this year.

In 2006, the year in sleep got off to a great start with the annual Sleep Medicine course.

Headed by Dr. Jim Parish, FCCP, last year's 3-day meeting was held in warm and sunny Scottsdale, AZ (where Dr. Parish lives and works at the Mayo Clinic). Over 250 attendees were present. Those in attendance received a focused overview of sleep medicine by an excellent faculty. Complementing the lectures were excellent clinical, case-based workshops in the midday.

AT PRESENT, THE THIRST FOR SLEEP MEDICINE KNOWLEDGE AND EDUCATION APPEARS TO BE UNQUENCHABLE.

The reviews of the course were excellent. The common theme of attendees when asked for ways to improve the course was that they wanted even more content.

Thus, plans were made to increase the course by half a day and add more material on the basics of polysomnography.

As I write this piece, I have just returned from the 2007 Sleep Medicine course, and it went very well again.

My impression is that there is an almost insatiable desire at the present time for sleep medicine education for pulmonary physicians (and others—attendees included neurologists; ear, nose, and throat surgeons; pediatricians; and other physicians).

This winter course meets that need for many people, and the course seems to have a bright future.

The sleep medicine education and training theme continued on through the rest of 2006.

The ACCP established its first ever Sleep Medicine Board Review Course. This course ran concurrently with the Critical Care Board Review Course during late August, in Orlando, FL.

The attendance was outstanding, with about 220 physicians of all ages and backgrounds paying rapt attention to speakers covering the world of sleep basic science and clinical medicine.

The lectures were supplemented with midday workshops that reinforced important scientific and clinical concepts with clinical case examples.

The number of attendees at the Sleep Medicine Board Review Course equaled that of the Critical Care Board Review Course.

So, at the end of the day, there were literally hundreds of pulmonary, critical care, and sleep medicine physicians walking around the Disney boardwalk and Epcot to watch fireworks, catch a quick meal, or purchase Disney World trinkets.

The usual Florida late-afternoon thunderstorms and a near-miss hurricane could not dowse the enthusiasm of the attendees at this course.

The CHEST 2006 conference in Salt Lake City, UT, contained excellent sleep medicine content, as usual, thanks to the input and work of the Sleep Medicine NetWork.

Beginning with a postgraduate course covering many important aspects of polysomnography monitoring, and continuing on to many other sessions in the general meeting that covered many aspects of clinical sleep medicine, CHEST 2006 was a very fulfilling meeting from a sleep medicine standpoint.

CHEST 2006 also continued the tradition, started nearly a decade ago, of holding a course for sleep medicine fellows the Saturday before the meeting. Attended by nearly 90 fellows-in-training, this extremely popular course continues to receive great reviews by all in attendance.

Finally, sleep medicine was included in the simulation center. The simulation center provided hands-on demonstrations of how to properly apply polysomnographic recording equipment on simulated patients.

This innovative approach to education at CHEST meetings is truly cutting-edge and contributes considerably to making CHEST a great meeting.

Looking ahead in 2007, sleep medicine education is continuing on the same strong trajectory established last year.

The winter Sleep Medicine course

Sleep Institute
American College of Chest Physicians

in Scottsdale, AZ, has successfully concluded, with approximately 240 attendees.

In late August 2007, the second Sleep Medicine Board Review Course will take place. This time, we will trade the heat and humidity of summer in Orlando, FL, for the heat without humidity in Phoenix, AZ.

For those of you who may be interested in taking the new Sleep Medicine Exam, a board review course is highly recommended, and the College's board review course is an excellent one.

(Full disclosure: I am the co-director of the board review course.)

We anticipate an even larger registration for this board review course than last year's course, with a similar roster of outstanding speakers and teachers.

The final area I will highlight is the Sleep Institute's Regional Sleep Education initiative.

Funded by a generous educational grant from Boehringer-Ingelheim Pharmaceuticals, the Sleep Institute has put together an excellent course to "take on the road."

In this case, the road refers to 20 different cities or metropolitan areas across the country.

The education is directed at primary care physicians and other frontline physicians or providers (including physician assistants and nurse practitioners). Each event is a half-day continuing medical education course that serves as a crash course in the essentials of sleep medicine for primary care physicians.

The curriculum is not intended to make attendees sleep medicine experts, but rather to enhance their knowledge about sleep and a few of its more common disorders. The lectures focus on obstructive sleep apnea, restless legs syndrome, and insomnia. The lectures are supplemented with clinical cases and discussion.

The settings are intentionally small, and attendance is limited to about 25 people, so that each attendee will have a chance to interact with the faculty and each other.

The goal is to improve the understanding of sleep disorders in each of these practitioners.

The curriculum is presented by a local pulmonary/sleep medicine expert, along with a visiting faculty member from the College.

At the end of the session, attendees are provided a toolbox with screening questionnaires and other measures they can employ everyday in their practices to help them better identify patients with sleep disorders.

The Sleep Institute believes these efforts are crucial to improving the overall care of patients with sleep disorders in our communities.

At present, family physicians, general internists, and other frontline physicians receive essentially no education in sleep disorders in their residencies, and only about 4 hours, on average, in the 4 years of medical school before residency training.

Whatever these physicians and other practitioners learn is generally through programs, such as this one.

Finally, the College is also developing assessment tools to be used in conjunction with this educational program in order to document attendees' level of knowledge prior to the course and then measure how much they learned from the course.

The College plans to follow these physicians over time and see how they have changed their practice as a result of this course.

This high level of educational outcomes monitoring truly characterizes the seriousness of the College's approach to education.

In summary, the College continues to be a leader in pulmonary, critical care, and sleep education in a variety of formats and styles.

In the case of sleep medicine education, the demand for high-quality courses is continuing to grow.

In 2006, nearly 500 physicians attended either the winter sleep course or the board review course (some attended both).

At present, the thirst for sleep medicine knowledge and education appears to be unquenchable, and the College is providing excellent offerings for those interested in this area.

I believe that 2007 will continue this trend. ■

Dr. Charles W. Atwood, Jr., FCCP
Section Editor
Sleep Strategies

AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

PATIENT INFORMATION ORGANIZATIONS

Pulmonary Hypertension Association Provides Hope

▶ **Mission:** *To seek a cure for pulmonary hypertension (PH) and provide hope for the PH community through support, education, advocacy, awareness, and research.*

According to National Institutes of Health Registry results, there were 187 patients in the United States diagnosed with primary (now idiopathic) PH in 1985. Five years later, three patients asked the National Organization for Rare Disorders (NORD) to help them locate other patients with PH. These patients went on to found the Pulmonary Hypertension Association (PHA), which has grown to over 7,000 members and 19,000 friends and supporters.

PHA members work together to raise awareness and funding to improve treatment and advance research. It has been estimated that there are more than 100,000 patients in the United States.

PHA offers a myriad of resources. It hosts a Web site (www.PHAssociation.org) and message boards. PHA supports nearly 140 support groups throughout the United States and offers a patient-to-patient telephone help line and the Patient's Survival Guide, a 280-page guide available in multiple languages. PHA produces print and electronic publications, including two member newsletters, a free diagnosis CD-ROM, and over a dozen other medical education DVDs. The PHA Scientific Leadership Council oversees the production of the world's only medical journal dedicated to PH, *Advances in Pulmonary Hypertension*, mailed quarterly to cardiologists, pulmonologists, and rheumatologists. PHA also promotes advocacy and awareness initiatives through targeted advocacy programs and media campaigns. ■

Visit www.PHAssociation.org/Medical.

ACCP Product of the Month: Sleep Medicine Board Review Syllabus

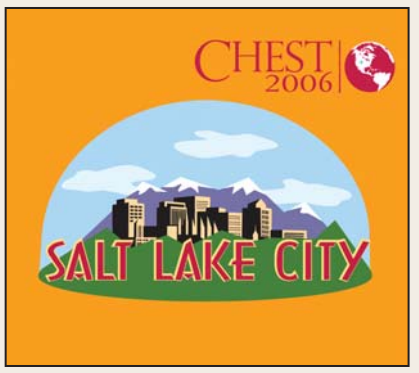
Taking the new sleep medicine board exam this fall? You'll want this CD-ROM. Straight from the 2006 ACCP Sleep Medicine Board Review Course, this syllabus covers every topic from the popular course in a concise, easy-to-use format. The CD-ROM contains the entire content of the book, plus search and navigate capabilities for the information you need. Use it to prepare for the new ABIM sleep medicine board examination or to keep abreast of new developments.

Search for other ACCP sleep-related courses and products at www.chestnet.org. ■

Now Available! CHEST 2006 Photos

Now is your chance to view and order photos from the Salt Lake City CHEST 2006 meeting.

Look through this outstanding array of CHEST 2006 impressions, and order for yourself, your family, or your friends and colleagues. Photos from special events, committee and NetWork meetings, fellows conferences, and more are now available at www.lagniappestudio.com/chest2006. ■



NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

Creating Healthy Work Environments: Authentic Leadership

BY DORRIE K. FONTAINE, RN, PHD, FAAN

Leaders must fully embrace the imperative of a healthy work environment, authentically live it and engage others in its achievement. (AACN 2005)

Physician and nurse leaders must work together to ensure that patients and families receive safe, compassionate, patient-focused care. As equal partners in directing the critical care environment, they can use the framework of authentic leadership to guide their practice. Authentic leadership is the glue that holds the **AACN Standards for Establishing and Sustaining Healthy Work Environments** together (www.aacn.org/HWE). ACCP's partnership with the American Association of Critical-Care Nurses to implement these standards will help to make healthy work environments a reality, promoting better morale and patient safety through our joint contributions.

Joanne Disch, a past AACN president, states that leadership is influencing others to take action to meet specific goals. It requires vision, as well as an ability to connect with others. She says that, in fact, the "connection" piece of authentic leadership may be most essential. Forming partnerships across disciplines, speaking up about current reality, and engaging others in the complex chaos of health care define authentic leaders.

Embracing a healthy work environment means not accepting the status quo. Leaders must let go of frameworks that no longer serve them and adopt ones that allow solutions and strategies to emerge from new thinking (Klein. *You Are the Leader You've Been Waiting For*. Encinitas, CA: Wisdom Heart Press, 2006). It is best to learn multiple perspectives to reframe challenging situations, including the structural, human resource, policy, and symbolic frames (Bolman and Deal. *Reframing Organizations: Artistry, Choice, and Leadership*. San Francisco, CA: Jossey-Bass, 2003). Envisioning a healthy work environment where the needs of patients and families drive the system is possible if outdated beliefs are dismantled.

AMERICAN ASSOCIATION of CRITICAL-CARE NURSES

Self-reflection is needed. Ask yourself: What are the talents I bring to creating a healthy work environment and leading the effort at the unit or hospital level? Among the skills identified within the "Authentic Leadership" standard are skilled communication, team building, being an agent for positive change, and role modeling for collaborative practice. Ask a colleague for feedback, and be open to new insights. Imagine the possibilities if physicians and nurses asked each other for feedback. An authentic physician leader demonstrates the attributes of a healthy work environment during rounds when nursing staff is recognized for its input and when communication is collegial and respectful of differing views.

The tactics of authentic leaders can be simple but powerful: making observations, asking questions, and offering interpretations. By not remaining silent, leaders show their courage in the face of personal challenges, especially in offering an alternative view (Heifetz and Linsky. *Leadership on the Line: Staying Alive Through the Dangers of Leading*. Boston, MA: Harvard Business School Press, 2002). A new role for authentic leaders is envisioned, one that places a primary value on understanding the complexity of the system, valuing dissent, and not taking comfort in organizational silence (Henriksen and Dayton. *Health Services Research*. 2006; 41:1539).

Engaging others is about making connections with a high degree of emotional intelligence. Authentic leaders use stories to share clear and compelling messages. Leaders need the characteristics of a clear purpose, unbending values, a compassionate heart and relationships, and real self-discipline (Shirey. *Am J Crit Care* 2006; 15:256). Developing leaders requires educational programs, role models, performance incentives to "act leader-like," and dedicated time. The journey to a healthy work environment begins with authentic leaders, physician and nurse partners, taking the first step. ■

www.aacn.org/HWE

DR. FONTAINE *is Associate Dean, Academic Programs, University of California School of Nursing, San Francisco. She is also a past president of AACN.*

Ambassadors' Antitobacco Message Reaches 2,000 Youth

Members of The CHEST Foundation's Ambassadors Group have addressed students in classrooms all over the world to discuss tobacco prevention and good lung health.

To date, more than 2,000 students, ages 8 to 18, have participated in lung health education programs presented by ACCP Ambassadors in their local communities and in locations worldwide. Many Ambassadors have presented in cities where their spouses are providing ACCP pro bono education.

Susan Kvale, Kathy Wilder, and Monir Almassi have been very involved and active in these Ambassadors educational initiatives and will offer a training session during CHEST 2007 on how to present these programs.

ACCP

The Ambassadors have reached students in Guatemala, Romania, Turkey, China, Poland, California, Michigan, Connecticut, New York, Wisconsin, and Alaska, among others.

The Lung Lessons™ program is a curriculum developed by The CHEST Foundation and used to teach youth about good lung health and the dangers of tobacco.

The school presentations can be supplemented with material from *Make The Choice: Tobacco or Health?* This speakers kit was created by the ACCP Women's Health NetWork as a way to help healthcare professionals and community members persuade women, teens, and adolescents to say no to tobacco.

Included in the kit are tips on effective antitobacco presentations, slides, resources, and more. Access the kit at http://speakerskit.chestnet.org/.

The Ambassadors Group is composed of anyone who wishes to support the goals of The CHEST Foundation through event participation, volunteer hours, networking, financial gifts, or tobacco prevention education. Members are usually spouses, friends, or children of ACCP members.

For more information or to join the Ambassadors Group, contact Sue Ciezadlo at sciezadlo@chestnet.org. ■

April 30 Foundation Awards' Deadline Nears

A valuable benefit of ACCP membership is available to you right now.

Nearly $1 million will be awarded to ACCP members in 2007 through The CHEST Foundation's Awards Program.

Monetary grants will be awarded for outstanding clinical research projects in many areas of chest medicine, exceptional leadership in end-of-life care, and in recognition of the pro bono service of ACCP members.

THE CHEST FOUNDATION

In addition, one ACCP member will be selected as the Second GlaxoSmithKline Distinguished Scholar in Respiratory Health and another ACCP member will be selected as the Second GlaxoSmithKline Distinguished Scholar in Thrombosis in 2007.

All applications are reviewed by ACCP members who have expertise and experience in the specific subject area of each award.

Enter The CHEST Foundation's Web site, www.chestfoundation.org, to find out all the criteria and requirements for the awards.

ACCP members may apply online, or download an application as a Word document, and mail or e-mail to Sue Ciezadlo (sciezadlo@chestnet.org) at The CHEST Foundation.

Some of the clinical research awards are for 2-year research projects, while others fund projects that are 1 year in length.

Both levels of the Humanitarian Awards, the Humanitarian Recognition Awards and the Humanitarian Project Development Grants, fund volunteer projects that provide needed medical care to people living in communities in the United States, Canada, and around the world.

Humanitarian Award recipients are honored each year at the Making a Difference Awards Dinner during the CHEST meeting.

The deadline for all applications is April 30, 2007.

Use this valuable benefit of your ACCP membership and apply today. ■

Pulmonary Perspectives

The CFC to HFA Transition for Albuterol

Part 2. HFAs: The Solution

Chlorofluorocarbon (CFC) propellants in metered-dose inhalers (MDIs) have no intrinsic medicinal value. They are only needed to formulate the drug in liquid form within the MDI canister and then to propel the active drug into an aerosolized form with actuation of the MDI.

CFCs are ideal propellants, because they are relatively inert and inflammable and have a very low order of toxicity. Over millions of patient exposures, CFCs have a demonstrated highly favorable safety record.

Regulatory agencies made clear that an alternative propellant must not only have the necessary physicochemical characteristics for drug formulation purposes, but must also not compromise the highly favorable safety and efficacy profile of albuterol.

The intent of the albuterol MDI reformulation process with hydrofluoroalkane (HFA) was to provide products that were environmentally safe and had comparable efficacy and similar safety as the CFC albuterol products. However, reformulation with HFA did require modifications of the MDI, some of which improved technologic performance of a device originally designed in the 1970s.

REASSURING PATIENTS THAT ALBUTEROL MDIs REFORMULATED WITH HFA HAVE A SIMILARLY FAVORABLE RISK BENEFIT PROFILE WILL BE AN IMPORTANT ASPECT OF THE TRANSITION PROCESS.

Essential Use Exemptions and Alternative Propellants

The Montreal Protocol banned not only CFCs, but also any ozone-depleting substance (ODS). Temporarily exempted from this ban were essential-use ODSs, defined generally as those necessary for health and safety or critical for functioning of society and for which there were no technically and economically feasible alternatives.

Essential uses are primarily CFCs for use in MDIs. The other ODS that presently receives essential use status in the United States is methylchloroform for use in space shuttles and Titan rockets. Each signatory nation of the Montreal Protocol can nominate volumes of ODSs to be used for essential purposes, on an annual basis, to the Protocol's Technical and Economic Assessment Panel.

In the United States, the Environmental Protection Agency is responsible for identifying essential-use nominations. The Food and Drug Administration (FDA) advises the Environmental Protection Agency on nominations for CFC volumes after reviewing use patterns of CFC MDIs, the need for future MDI supplies, and CFC stockpiles.

Eventual development of replacement propellants for CFCs was expected under the Protocol, but this has been a lengthy process.

In 1989, MDI manufacturers joined the Pharmaceutical Aerosol CFC Coalition (PACC). PACC viewed HFAs as potentially acceptable replacement propellants, because, like CFCs, they are relatively inert and nontoxic. HFAs have a halocarbon global warming effect, but less than that of CFCs.

PACC eventually formed the International Pharmaceutical Aerosol Consortium for Toxicology Testing of HFA -134a (IPACT-1) and HFA-227a (IPACT-ll), which were tasked with performing the toxicologic and clinical testing necessary to obtain regulatory approval for use of these alternative propellants in MDIs.

These collaborative efforts led to an extensive toxicologic effort that confirmed that exposure to HFA resulted in no clinically meaningful safety concerns. These safety data formed the basis of Drug Master Files, which are accessible by member companies and have been filed with regulatory agencies worldwide as a reference to support marketing applications for individual reformulated products. HFA-134a has been used for the reformulation of albuterol.

As individual products were being reformulated in HFAs, the FDA developed a framework for determining when essential-use status for CFC MDIs would be terminated.

In 2006, the FDA stipulated that essential-use status for CFC albuterol MDIs would be withdrawn after 2008, based on the availability of three HFA albuterol MDIs and an HFA MDI with levalbuterol. The CFC-to-HFA transition for albuterol in the United States comes after Australia, Canada, Japan, and the European Union have designated CFC a nonessential use for albuterol.

Interestingly, the transition for albuterol comes at the same time as a precipitous decline in CFC availability for use in the United States. The United States received exemptions to use about 3,500 metric tons of CFC in 1996, 3,300 metric tons in 2002, but only about 1,000 tons, with 70% for albuterol MDIs, in 2006. In addition, Honeywell, the only producer of CFCs acceptable to the FDA, closed its manufacturing facility in the Netherlands in 2005.

Full transition to HFA albuterol in the United States is possible before the end of 2008 due to unavailability of CFCs.

Development of HFA Albuterol Products

In 1994, the FDA published guidelines for clinical development plans necessary to support new drug applications for reformulated inhaled products (Points to Consider, FDA Sept 19, 1994).

The recommended plan for albuterol included a small safety and tolerability study, a dose ranging study, a 12-week pivotal safety and efficacy study, and a 1-year safety study. Additional studies were required to demonstrate efficacy in protecting against exercise-induced bronchospasm, safety and efficacy in children, and safety and efficacy when switching patients from a CFC albuterol to an HFA albuterol.

Generally, approved HFA albuterol products have followed this study approach (*J Allergy Clin Immunol* 1995; 96:50; *Chest* 1998; 113:290; *Ann Allergy Asthma Immunol* 1997; 79:85; *J Asthma* 2000; 37:667; *J Asthma* 1999; 36:107). These clinical trials generally included three treatment arms, HFA albuterol, HFA placebo, and a CFC albuterol active comparator.

The objectives of these studies were to show that HFA albuterol provided significantly better bronchodilation than HFA placebo and comparable bronchodilation as CFC albuterol. Studies to determine whether the HFA albuterol provided equivalent bronchodilation, a much more rigorous requirement, were not expected by the FDA but performed for individual products (*Am J Respir Crit Care Med* 1999; 160:354). The inclusion of an HFA placebo arm allowed clinical safety of the propellant to be assessed. The safety profile of HFA albuterol was expected to be similar to that seen with CFC albuterol.

Reformulation of albuterol in HFA required new seal elastomers and redesign of MDI metering valves. These steps changed many features of MDI performance.

Propellant loss from the metering chamber between uses has been reduced, resulting in less frequent need for reprimming with HFA MDIs. Less active drug is lost from the metering chamber between actuations (through creaming of drug out of suspension), reducing the puff-to-puff variability in drug content. Drug delivery tapering at the end of device life may be more abrupt, allowing patients to recognize more quickly that their MDI is empty.

HFAs have higher moisture affinity than CFCs. This favors water seeping around the metering valve gaskets into the canister. One albuterol product requires a moisture-resistant protective pouch and has a shorter shelf life. There are differences among albuterol HFA MDIs in the excipients added to the propellant formulation. One HFA albuterol product contains a small amount of ethanol. This small amount will not have a discernible clinical effect but may be of concern for patients of particular religious beliefs and may result in a transient increase in breath alcohol levels after use.

Patients may notice a different taste with HFA albuterol, probably due to the propellant. Some HFA albuterol products have a warmer spray, which will result in less of a cold effect, as felt with CFCs. An HFA albuterol MDI spray may also feel different, because ballistic characteristics of the aerosol plume emitted from the actuator have been changed.

Some products have a spray with less force and a smaller plume size. At the usual dose of two puffs, this difference will not affect bronchodilation effect, because HFA albuterol MDIs were specifically designed to provide the same amount of albuterol, 90 mcg per puff, in a suspension aerosol with the same particle size distribution as CFC albuterol MDIs. It is possible, though, that a less forceful spray might result in small, but noticeable, differences in lung delivery with higher cumulative doses of HFA albuterol or when HFA albuterol is used with a spacer.

Clogging of HFA albuterol actuator has been reported and is a potential problem for all MDIs. With proper cleaning of the actuator, according to manufacturer's instructions, MDIs should perform reliably. If a noticeable reduction in the force of the emitted spray is noted by the patient, the actuator should be recleaned.

Patients should be advised not to immerse the canister in water to determine whether the canister is empty. It is not a reliable method for determining remaining doses in the MDI, and water may enter the canister stem and obstruct the spray (*Chest* 2004; 126:1134).

Conclusion

Patients will recognize the transition from CFC to HFA albuterol MDIs. HFA albuterol products will have a different taste and feel than CFC albuterol MDIs. Reassuring patients and health-care providers that albuterol MDIs reformulated with a new propellant have a similarly favorable risk-benefit profile as CFC albuterol will be an important aspect of the transition process for health-care providers.

Ironically, although reformulation of albuterol in HFA was not intended to provide a medical advantage, there will be financial benefits to the pharmaceutical industry, because the transition from CFC to HFA albuterol will also mean the transition from the current, less expensive, generic CFC albuterol products to more expensive, branded HFA albuterol products. ■

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Tranfusion-Related ALI Still Escapes Notice

The current diagnostic criteria exclude an entire class of patients, an expert contends.

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

BARCELONA — Transfusion-related acute lung injury probably remains underrecognized worldwide, despite recent clinical definitions and diagnostic guidelines, Dr. Antonio Artigas said at the annual congress of the European Society of Intensive Care Medicine.

"The disorder occurs in a heterogenous population, and the current definition excludes any patient with a pre-existing acute lung injury," said Dr. Artigas, director of the critical care center and department of intensive medicine at the Parc Taulí Hospital Consortium in Barcelona. "I believe the major consequence of this is a large underestimation of this disease."

The current diagnostic criteria, adopted at a 2004 consensus conference in Toronto, apply only to patients with no prior acute lung injury. Transfusion-related acute lung injury (TRALI) is diagnosed when there is acute onset of respiratory distress within 6 hours of a transfusion, with hypoxemia, bilateral lung infiltration on x-ray, no evidence of circulatory overload, and no other temporally associated acute lung injury risk factor.

Unfortunately, Dr. Artigas said, this definition leaves out an entire class of patients: those with pre-existing acute lung injury who develop new or worsening symptoms after a transfusion. TRALI's radiologic and pathophysiologic characteristics, which are very similar to other acute lung injuries, may also confuse the diagnostic picture, he said.

TRALI accounts for only about 3% of the etiologies of acute lung injury, and most patients recover with supportive measures within 96 hours. But it is the leading cause of transfusion-related death in the United States.

The United States also has a higher frequency of TRALI, with about one case per 5,000 units transfused, compared with one case per 7,900 units transfused in Europe. "There are about 300 reported TRALI deaths each year in the U.S., although again, I think the number is probably higher because it is underrecognized," said Dr. Artigas.

There is no definitive laboratory test to identify TRALI. Some markers are helpful, including a transient acute leukopenia, a leukocyte antigen/antibody interaction between the donor and recipient, HLA antibodies in donor or recipient plasma, and an edema fluid/plasma protein ratio of more than 0.75. There may also be an increase in cell priming activity in polymorphonuclear leucocytes in the blood product.

This clinical picture hints at the presumed mechanism behind TRALI: stimulation of the recipient's inflammatory response, by either antibodies or inflammatory cytokines in the transfused blood products.

Not surprisingly, patients who undergo massive transfusions (more than eight units) are at significantly increased risk, compared with those who receive fewer units.

"We know that there are some other predisposing factors, including recent surgery, hematologic malignancy, chemotherapy, oncologic surgery, bone marrow or solid organ transplant, and all patients who are already at risk of developing an acute lung injury," Dr. Artigas said.

Prevention efforts have been aimed at reducing inflammatory markers in stored blood products—a task that is not easily accomplished, he said.

Some countries have considered screening processes to decrease the risk, including not accepting donations from multiparous women—who may have higher levels of HLA antibodies—and deferring donors with high plasma levels of inflammatory cytokines.

Both strategies have problems, however: Deferring all multiparous women would have a significant impact on the supply of blood, and on-site inflammatory marker screening would be very costly, Dr. Artigas said.

Decreasing storage time for blood products is probably the most practical approach, because cell priming activity is lower in fresher product.

"It's best to use blood that has been stored for a period of less than 2 weeks," he recommended.

Some studies have suggested that leukoreduced blood may be safer, although Dr. Artigas reported unpublished data from a trial that did not support this idea. The randomized controlled trial of 268 trauma patients found no difference in TRALI rates between those who received transfusions of leukoreduced and those who received untreated blood products. ■

CLASSIFIEDS

Thoracic Surgery Faces Future Workforce Dilemma

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Tougher times loom ahead for the thoracic surgery profession, according to the findings of a national workforce study conducted by the Association of American Medical Colleges.

"I think there are some very difficult, brutal facts, which you have to come to terms with," Dr. Atul Grover, FCCP, warned in presenting the results at the annual meeting of the Society of Thoracic Surgeons.

Thoracic surgery is a specialty in a bind. Applications to training programs by U.S. medical school graduates are down. Trainees report difficulty in finding a suitable position upon graduation, reflecting a current practitioner surplus. Meanwhile, demand for coronary artery bypass graft (CABG) surgery—a bread-and-butter operation for the specialty—has declined sharply.

The flip side of the problem is that the thoracic surgery workforce is getting on in years. While roughly one-third of U.S. physicians overall are aged 55 or older and hence likely to retire in the next 10-15 years, that's true of 54% of the 4,800 board-certified thoracic surgeons now active in providing patient care.

The majority of thoracic surgeons in the 55-and-older group plan to retire between 2011 and 2015—just as a huge wave of baby boomers reaches age 65 and starts placing much heavier demands on the health care system. Today's 75- to 80-year-olds use twice as many physician services as similar-age patients did 20 years ago, a trend expected to be further accentuated when the baby boomers hit that age bracket, explained Dr. Grover, an internist and hospitalist who is associate director of the Center for Workforce Studies at the AAMC.

Making projections regarding future demand for physician services is fraught with uncertainty, but the most likely scenario according to the AAMC analysts is a roughly 50% increase in demand for thoracic surgery services over the next decade.

"Between now and 2025, the likely range of demand is going to be 1,000-2,000 thoracic surgeons higher than the number available if we increase the number of new trainees to 150 per year from the current 129," he said.

Dr. Grover predicted that the overall impact of the decline in CABG procedures is unlikely to be the calamity many cardiothoracic surgeons fear. Medicare claims data for 1999-2004 showed a 10% drop in CABG claims, but at the same time, there was a near doubling of claims for valve operations and other non-CABG heart procedures, along with a 25% rise in general thoracic procedures.

The AAMC surveyed 50 top interventional cardiologists, thoracic surgeons, and interventional radiologists, not one of whom said that they thought CABG will disappear altogether; more likely, the current CABG rate will stabilize or decline to a rate similar to that found in Canada, England, Germany, and other developed countries, which is about half the U.S. rate.

In 2004, thoracic surgeons averaged 163 procedures overall, down from a peak of 178 in 1997 but essentially the same as in 1993.

If the CABG rate stabilizes and the number of other thoracic surgical procedures increases as anticipated, the nation would need about 250 trainees graduating per year to accommodate demand. The challenge now, according to Dr. Grover, is to attract physicians to the specialty in order to meet tremendous future demand despite relatively low current requirements.

The 14-month workforce study was conducted in conjunction with the Society of Thoracic Surgeons and the American Association for Thoracic Surgery. ■

Dr. Robert J. Cerfolio, FCCP, comments: *Although the number of applicants for cardiothoracic fellowship positions has decreased, this is nothing more than the natural ebbs and flows that occur in all specialties over time. The glory days that we have enjoyed over the past 30 years will return. Soon, once again only the best and the brightest will be able to obtain a spot in our limited training programs. They know that a life as a cardiothoracic surgeon features challenging yet rewarding technical operations, in a well-protected specialty that is well reimbursed, with a good lifestyle, and grateful patients. What more could anyone ask?*

Dr. Peter McKeown, FCCP, comments: *While the implementation of drug-eluting stents has had a dramatic short-term impact in reducing the volume of cardiac surgery, this is unlikely to diminish the need for more cardiothoracic surgeons in the future. Also, careful analyses of randomized trials comparing stents to CABG tend to favor surgery in the long run. These interventions should be seen as complementary and supplementary. Indeed, the future of cardiac surgery lies in a closer relationship with our cardiology colleagues, interventional radiologists, tissue engineers, and gene therapists.*

Selected Elderly Can Benefit From Lung Cancer Surgery

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

STOCKHOLM — Advanced age should not preclude octogenarians from surgery for non–small cell lung cancer, reported Dr. Alberto Dominguez-Ventura at a meeting of the European Association for Cardio-Thoracic Surgery.

Researchers at the Mayo Clinic in Rochester, Minn., reviewed the charts of 294 pulmonary resection patients ages 80-94 and found that about a third (34%) survived 5 years.

Analysis showed that women had a slightly better 5-year survival rate than men: 36.2% vs. 32.7%, according to Dr. Dominguez-Ventura, a thoracic surgeon at the Mayo Clinic.

Patients who underwent lobectomy or bilobectomy fared best with a 5-year actuarial survival rate of 41%, he said. Among those who underwent segmentectomy/wedge resection, the 5-year survival rate was 24%. Only 11% of pneumonectomy patients were alive at 5 years.

There are no studies to show what happens to patients with non–small cell lung cancer who do not qualify for surgery, but mortality is 100%, Dr. Dominguez-Ventura said in an interview at the meeting, which was held with the European Society of Thoracic Surgeons.

Octogenarians "can have meaningful long-term survival and benefit from surgery, but you have to select your patients," added Dr. Stephen D. Cassivi, a thoracic surgeon, surgical director of lung transplantation at the Mayo Clinic, and coinvestigator in the Mayo study.

"Their age becomes a consideration, but it is not a deal breaker," he said in an interview at the meeting, calling for thoracic surgeons to evaluate octogenarians in much the same way as they would evaluate any other candidate for lung cancer surgery.

Dr. Dominguez-Ventura said he undertook the investigation because octogenarians are the fastest-growing segment of the population and a group for whom lung cancer is a leading cause of death.

"We are going to see a lot more of them," he said.

The population of patients reviewed—192 men and 102 women—underwent thoracic surgery from January 1985 to August 2002 at the Mayo Clinic. Their median age was 82. Median follow-up was 2.2 years with a range of 1 month to 13.6 years.

None of the patients was lost to follow-up, and Dr. Dominguez-Ventura said that he was able to find the cause of death for two-thirds of the patients. Half died of cancer, he said, and half of other causes.

About 6% died during surgery. Nearly half of the patients (48%) had perioperative complications. The most common was atrial fibrillation, observed in 21% of patients.

Although comorbidities were common, Dr. Dominguez-Ventura reported that none proved to be a significant predictor of outcomes. Not even preoperative impairment of forced expiratory volume in 1 second (FEV_1) appeared to influence survival.

One presenting symptom stood out, however. No patient with dyspnea survived 5 years, whereas 35% without dyspnea were alive at 5 years.

Most of the patients (72%) were asymptomatic, according to Dr. Dominguez-Ventura. Two-thirds were stage I. Not surprisingly they had better survival (IA, 48%, and IB, 39%) than patients who were stage II (IIA, 17%, and IIB, 23%) or stage III (IIIA, 9%, and IIIB, 0%), he said.

Only two patients had chemotherapy. Dr. Cassivi said that most of the patients would not have been eligible to receive chemotherapy.

"Usually they are turned down or too sick to tolerate it," he said, adding that it is rare for octogenarians to qualify for radiotherapy.

Although the elderly are more prone to complications, and their survival rates may not be as high as those of younger patients, he recommended that they be given an opportunity to qualify for surgery.

"Surgery is still the best treatment for lung cancer," he said. ■

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*For gram-negative infections due to susceptible strains of indicated organisms in treating moderate-to-severe pneumonia.

MAXIPIME is contraindicated in patients who have shown an immediate hypersensitivity reaction to MAXIPIME, cephalosporins, penicillins, or any other β-lactam antibiotics.

In North American clinical trials of MAXIPIME at a dose of 0.5 to 2 g IV q12h, the most common adverse events were local reactions (3%), including phlebitis (1.3%), pain and/or inflammation (0.6%); rash (1.1%). Pseudomembranous colitis has been reported with nearly all antibacterial agents, including MAXIPIME, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to administration of antibacterial agents.

HCAP defined as: healthcare-associated pneumonia.

Please see brief summary of prescribing information on adjacent page.