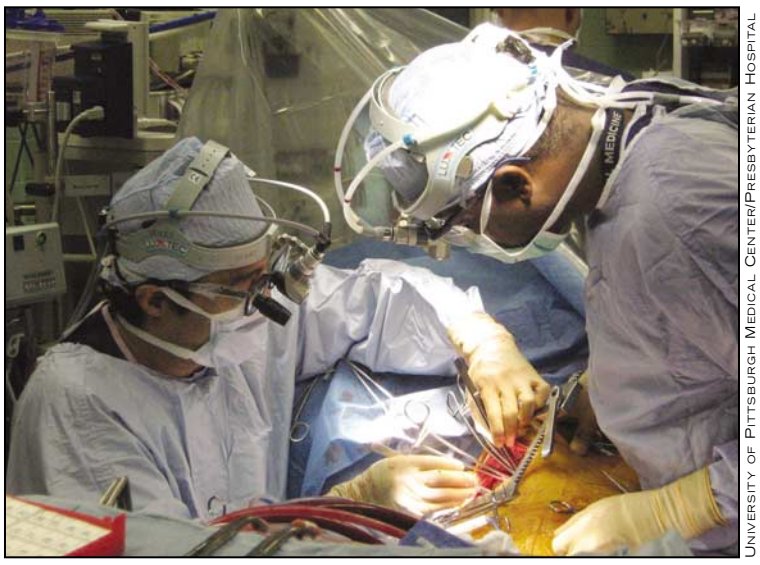
VOL. 3 • NO. 5 • MAY 2008

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



UNIVERSITY OF PITTSBURGH MEDICAL CENTER/PRESBYTERIAN HOSPITAL

The technique causes less pain than conventional approaches while delivering very similar survival rates, Dr. Yoshiya Toyoda said.

Anteroaxillary Approach Aids Lung Transplant

BY MITCHEL L. ZOLER
Elsevier Global Medical News

BOSTON — A novel, minimally invasive approach for lung transplant surgery produces small, cosmetically superior incisions and causes less pain than the conventional surgical method, according to results from a series of 116 patients.

In 68 patients treated with an anteroaxillary approach and 48 patients treated with a conventional approach, survival rates to 180 days after surgery were very similar—more than 90% in both groups. Patients in the anteroaxillary group were more likely to be extubated within 48 hours of surgery and less likely to need mechanical ventilation for more than 5 days, Dr. Yoshiya Toyoda reported at the annual meeting of the International Society for Heart and Lung Transplantation.

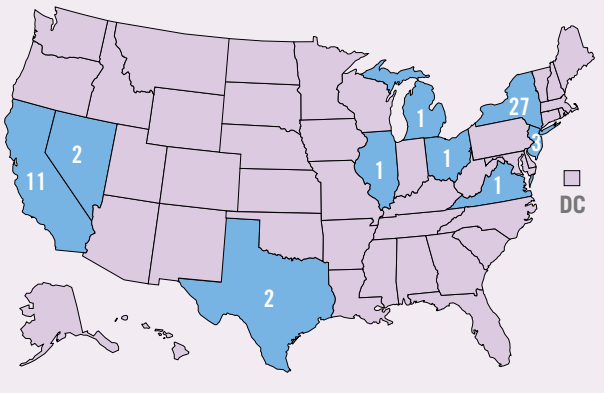
The anteroaxillary approach also preserved bilateral internal mammary arteries and the sternum, permitted rapid use of cardiopulmonary bypass, resulted in quick chest closure because of a small incision, and required less manipulation of the heart and phrenic nerve.

Because of these and other advantages, the anteroaxillary approach has become the standard surgical method used for lung transplants at the University of Pittsburgh Medical Center, where Dr. Toyoda is a thoracic surgeon and head of cardiopulmonary transplantation.

See **Transplant** • *page 2*

VITAL SIGNS

Number of Reported Cases of Extensively Drug-Resistant Tuberculosis



Note: Based on 1993-2006 data.
Source: Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS

Study Links Gene Variation, Biomarker To Asthma Risk

Serum levels of YKL-40 protein elevated.

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

A protein linked to inflammation and tissue remodeling is a significant biomarker for asthma and poor lung function, and a variation in that protein's genetic code also is associated with asthma risk and bronchial hyperresponsiveness, according to a study published in the New England Journal of Medicine.

A single-nucleotide polymorphism (SNP) was associated with elevated serum levels of the protein, YKL-40, in several populations, and both the genetic variation and elevated YKL-40 levels were associated with asthma, bronchial hyperresponsiveness, and reduced lung function, according to Carol Ober, Ph.D., of the University of Chicago and her associates in the United States and Germany (N. Engl. J. Med. 2008;358:1682-91).

In an earlier study, some of the same investigators had reported that serum levels of YKL-40 were elevated in patients with asthma. Serum YKL-40 levels also were associated with asthma severity, thickness of the subepithelial basement membrane, and pulmonary function, suggesting that YKL-40 levels could be a biomarker for asthma.

To identify genes that influence serum levels of YKL-40, the investigators conducted a genomewide association study in a group of 632 related Hutterites 6-92 years old (mean age 33) living in communal farms in South Dakota. They also included studies of children with and without asthma.

The investigators hypothesized that "variation in associated genes influences the risk of asthma and bronchial hyperresponsiveness, and is associated with reduced lung function."

In the current study, they found that among the Hutterites, mean YKL-40 levels

See **Biomarker** • *page 2*

INSIDE

Guidelines: No to Routine CT Screening

BY FRAN LOWRY
Elsevier Global Medical News

HOLLYWOOD, FLA. — Routine use of computed tomography screening for non–small cell lung cancer is deemed not ready for prime time in updated guidelines announced at the annual conference of the National Comprehensive Cancer Network.

The guidelines committee on non–small cell lung cancer (NSCLC) chose not to endorse CT screening despite recent data from the International Early Lung Cancer Action Program (I-ELCAP) showing the technology can detect stage I lung cancer.

"We don't recommend it routinely. We've included [two key] references regarding this, and we all await the national study which should be out in 2009 for the routine use, if needed, for spiral CT," said Dr. David S. Ettinger, FCCP, Alex Grass Professor of Oncology and professor of medicine, radiation oncology, and molecular radiation sciences at Johns Hopkins University, Baltimore.

The first study screened 31,567 asymptomatic individuals at risk for lung cancer at three different time points (N. Engl. J. Med. 2006;355:1763-71). The investigators concluded that annual spiral CT screening can detect lung cancer that is curable.

The second study presented a longitudinal analysis of 3,246 asymptomatic current or former smokers who were screened for lung cancer in 1998 and followed for a median of 4 years (JAMA 2007;297:953-61).

See **CT Screening** • *page 4*

CHEST PHYSICIAN
60 Columbia Rd., Bldg. B
Morristown, NJ 07960
CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

Genes and Asthma

Biomarker • *from page 1*

were 15% higher among those with asthma and 10% higher among those with bronchial hyperresponsiveness, compared with controls. They also found a significant association between an SNP in CHI3L1, a gene encoding for YKL-40, and elevated serum YKL-40 levels, asthma, bronchial hyperresponsiveness, and measures of pulmonary function.

In addition, the researchers determined that the same SNP was predictive of asthma from birth through age 5 years in a study of 638 German children, and in a study of 296 adults and children in Chicago.

The result "shows that serum YKL-40 level is a highly heritable, quantitative trait in humans and confirms that YKL-40 is a significant biomarker for asthma susceptibility and reduced lung function," the authors wrote. In addition, genetic variation in CHI3L1 "influences serum YKL-40 levels and is associated with the risk of asthma, bronchial hyperresponsiveness, and reduced lung function."

Identifying the rest of the genetic loci that contribute to the differences in serum YKL-40 levels and related proteins "could identify additional genes with a significant effect on the risk of asthma and lung function," the researchers added.

The findings suggest that the investigators have identified an important genetic risk factor for asthma, but the results need to be confirmed with large studies, Miriam Moffatt, D.Phil., and Dr. William O.C.M. Cookson of the National Heart and Lung Institute at Imperial College, London, said in an accompanying editorial (N. Engl. J. Med. 2008; 358:1725-6).

Survival Rates Similar

Transplant • *from page 1*

Dr. Toyoda reviewed his experience performing single- or double-lung transplantation at the university since the start of 2006. The conventional surgical approach, used in 48 patients, usually consisted of a posterolateral thoracotomy for single-lung transplantation, or a clamshell approach for double-lung transplantation.

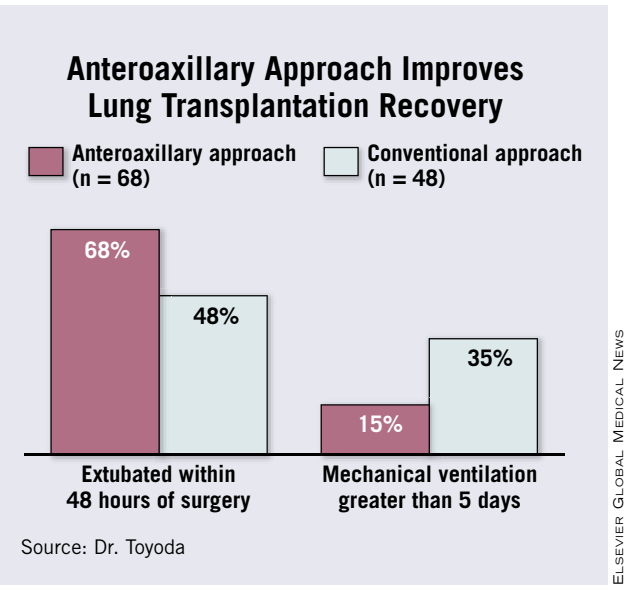
Since the new approach was first used last year, it has been performed on 68 patients, including 60 of 63 consecutive patients treated through April 2008. This series included 23 patients (34%) aged 65 or older, of whom 10 patients were aged 70 or older. The oldest patient he has treated with the anteroaxillary approach was 81.

In the anteroaxillary approach, the patient is in a supine position with arms fixed in front of the face. An 8- to 12-cm incision is made far from the sternum, parallel to the intercostal spaces.

The survival rate to 180 days following surgery was 91% in the patients treated by the anteroaxillary route and 92% in patients having conventional surgery.

The anteroaxillary approach led to a significant increase in the rate of patients becoming extubated within 48 hours of surgery (68% vs. 48% of those having conventional surgery), and a significant drop in the rate of mechanical ventilation greater than 5 days (15% vs. 35%). The average hospital length of stay was shorter with the anteroaxillary approach, 31 days, compared with 37 days with standard surgery, but this difference was not significant.

The only contraindications to use of the anteroaxillary approach are in patients who require multivessel coronary artery bypass surgery, and patients who need aortic repair in the region from the aortic root to the arch, Dr. Toyoda said.

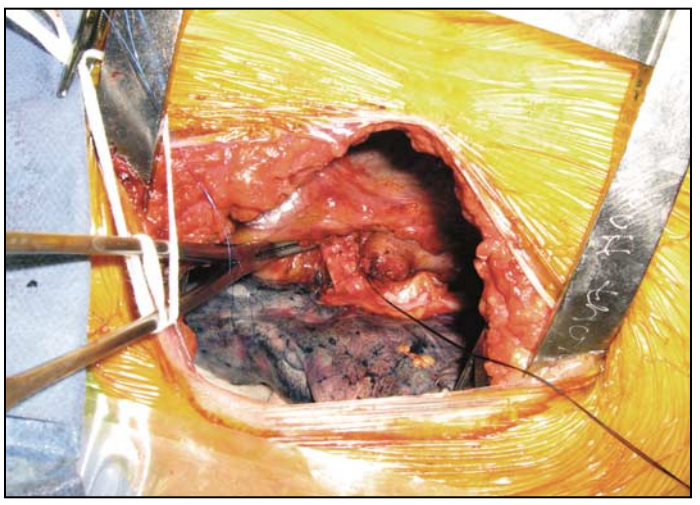


ELSEVIER GLOBAL MEDICAL NEWS

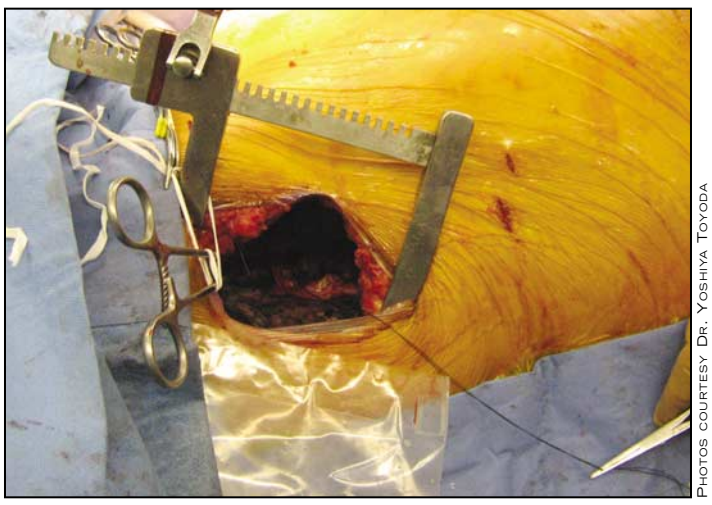
IN THIS ISSUE

CHEST PHYSICIAN Is Online

CHEST PHYSICIAN is available on the Web at www.chestnet.org/about/publications.



Anteroaxillary incision shows bronchial and pulmonary arterial anastomoses for lung transplantation.



Anteroaxillary incision on the patient's right side was used as part of a double-lung transplantation.

PHOTOS COURTESY DR. YOSHIYA TOYODA

AMERICAN COLLEGE OF CHEST PHYSICIANS®

CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group and Elsevier Global Medical News. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

The statements and opinions expressed in **CHEST PHYSICIAN** do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Elsevier Society News Group, a division of Elsevier Inc., do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

Address Changes: Fax changes of address (with old mailing label) to 973-290-8245.

POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

E-mail: chestphysiciannews@chestnet.org

ELSEVIER SOCIETY NEWS GROUP, A DIVISION OF INTERNATIONAL MEDICAL NEWS GROUP

President, IMNG Alan J. Imhoff
Director, ESNG Mark Branca
Executive Director, Editorial Mary Jo M. Dales
Executive Editor, IMNG Denise Fulton
Executive Editor, EGMN Kathy Scarbeck
Publication Editor Terry Rudd
Publication Associate Editor Jay C. Cherniak
VP, Medical Education Sylvia H. Reitman
Senior Director, Marketing and Research Janice Theobald
Circulation Analyst Barbara Cavallaro
Executive Director, Operations Jim Chicca
Director, Production and Manufacturing Yvonne Evans
Production Manager Judi Sheffer
Art Director Louise A. Koenig
Display Advertising Manager The Walchli Tauber Group: 443-512-8899, fax 443-512-8909, gary.walchli@wt-group.com, stephen.tauber@wt-group.com
Classified Sales Manager Rhonda Beamer, 443-512-8899, fax 443-512-8909, rhonda.beamer@wt-group.com
ADVERTISING OFFICES 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250
CLASSIFIED ADVERTISING OFFICES The Walchli Tauber Group, 2225 Old Emmorton Rd., Suite 201, Bel Air, MD 21015, 443-512-8899
EDITORIAL OFFICES 5635 Fishers Lane, Suite 6000, Rockville, MD 20852, 240-221-4500, fax 240-221-2541

Son-to-Father Avian Flu Transmission Reported in China

A quarter of avian flu cases have occurred in clusters of two or more epidemiologically linked people.

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

A report of avian flu spreading from son to father in China has raised concerns that person-to-person transmissions of the H5N1 strain of the influenza A virus could increase over time, according to an article published April 8 in the Lancet.

Investigators from the Chinese Centre for Disease Control and Prevention in Beijing reported that the two family members were diagnosed in December 2007 in China's Jiangsu Province. The 24-year-old son died of the infection, which he appeared to have contracted at an open poultry market.

The researchers determined that the son was the only plausible exposure of the 52-year-old father. He survived after receiving early antiviral treatment and plasma from a woman who had been vaccinated against H5N1 in a phase I clinical trial.

"H5N1 clusters require urgent investigation because of the possibility that a change in the epidemiology of H5N1 cases could indicate that H5N1 viruses have acquired the ability to spread more easily among people," Professor Yu Wang and his colleagues concluded (Lancet 2008 April 8 [Epub doi:10.1016/S0140-6736(08)60493-6]).

They noted that one-fourth of 376 avian flu cases reported as of April 2, 2008, occurred in clusters of two or more epidemiologically linked people. Since November 2003, a total of 238 deaths have been reported in 14 countries, the authors wrote.

In an accompanying comment, Dr. Jeremy Farrar observed that published reports of person-to-person transmission have so far been limited to health workers and to genetically related individuals. He questioned whether host genetic factors along with the "intensity and intimacy of contact between family members" might play a role in susceptibility.

"Whatever the underlying determinants, if we continue to experience widespread, uncontrolled outbreaks of H5N1 in poultry, the appearance of strains well adapted to human beings might be just a matter of time," warned Dr. Farrar of the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam and two coauthors (Lancet 2008 April 8 [Epub doi:10.1016/S0140-6736(08)60494-8]).

"In the meantime, all family contacts of a patient with probable or confirmed H5N1 should be given chemoprophylaxis and placed under surveillance," the comment advised. "Personal protection and advice must be extended to the family members and health workers visiting and looking after patients in hospital."

Acknowledging that "tension around emerging infections has led to often acrimonious and dispiriting debates" over the sharing of samples and international collaboration, Dr. Farrar hailed the new study both as a superb piece of epidemiologic work and a model of how collaboration can combat shared threats to world health.

ALL 91 CLOSE CONTACTS OF THE FATHER AND/OR THE SON WHO GAVE CONSENT FOR SEROLOGIC INVESTIGATION TESTED NEGATIVE FOR H5N1 ANTIBODIES.

In the detailed study reported by Professor Yu Wang, 100 people who had a close exposure to the father and/or the son infected with H5N1 were closely followed for 10 days. Of these, 91 people gave consent for serologic investigation.

The investigators reported that 78 (86%) received oseltamivir chemoprophylaxis. Two people—the son's girlfriend and a doctor—were mildly ill during the 10 days, but both tested negative for H5N1, and all 91 close contacts tested negative for H5N1 antibodies. H5N1 viruses were isolated only in the father and the son, and these were "genetically identical except for one non-synonymous nucleotide substitution."

The father received 75 mg of oseltamivir orally as chemoprophylaxis when the son's illness was identified. He was hospitalized the following day with fever, mild thrombocytopenia, and bilateral pneumonia. Doctors treated him with levofloxacin, corticosteroids, and 150 mg of oseltamivir orally, twice daily for 5 days . On day 3, he was started on 100 mg of rimantadine orally twice daily for 5 days. His respiratory status became worse, however, and he required positive pressure ventilation. His condition did not improve until after he received two 200-mL transfusions of plasma from the woman who had been given two doses of inactivated whole-virion H5N1 vaccine in a clinical trial. The investigators reported the father's fever resolved that night. He was discharged 22 days after hospital admission. ■

In Elderly, D-Dimer Tests Lose Some VTE Predictive Power

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

ATLANTA — Elderly people have much higher rates of venous thromboembolism than younger people do. They also tend to have elevated levels of D-dimer—which can make D-dimer testing less useful in predicting the risk of recurring blood clots when patients are aged 65 and older.

The relationship between exponentially increasing venous thromboembolism (VTE) rates in the elderly and rising D-dimer levels presents a diagnostic dilemma, according to speakers at a symposium on how thrombosis in the elderly presents "a public health and scientific problem of unrecognized dimensions."

"Older age reduces the clinical usefulness of D-dimer testing. … We probably need age-adjusted cutoffs in older people," Dr. Kenneth A. Bauer, a professor of medicine at Harvard Medical School, Boston, said during the special session at the annual meeting of the American Society of Hematology.

Incidence of venous thromboembolism rises exponentially starting at age 45 years.
DR. CUSHMAN

"We really do need more work done in D-dimer, though it is the most promising of the markers that we see in predicting recurrence risk," said Dr. Bauer, who is also chief of the hematology section at the Veterans Affairs Boston Healthcare System and director of thrombosis research at Beth Israel Deaconess Medical Center, Boston.

Incidence of venous thromboembolism rises exponentially starting at age 45 years, reported Dr. Mary Cushman of the University of Vermont, Burlington. VTE is three times more common in people aged 65 years and older, compared with those aged 45-64 years. When VTE patients are stratified by age, 70% are 60 years and older.

Just why VTE incidence increases with age is not clear, but Dr. Cushman offered several hypotheses: increased comorbidities and frailties, impaired mobility, inflammation, alteration of vein health, sarcopenia, and increased coagulation potential.

Despite limited data, she said, the evidence to date makes clear that the impact is also worse in the elderly, with rates of death, recurrence, post-thrombotic syndrome, and treatment complications rising with each decade of life. The elderly "are more likely to fail treatment than those under age 65," she said.

In healthy elderly individuals, however, researchers have found high levels of many coagulation activation markers, including D-dimer, a fibrin degradation product released when blood clots.

"D-Dimer really is a composite of thrombin activation and then plasma dissolution of the fibrin that is normally formed. There are low levels of D-dimer that we measured in normal healthy people," Dr. Bauer said.

The fact that D-dimer is heterogeneous has led to issues in using and standardizing D-dimer assays, he noted, contrasting it with other coagulation markers that are discrete polypeptides with defined molecular weights.

"D-dimer is a physiological variable and can vary over time," Dr. Bauer said, discussing a study of centenarians conducted in Italy (Blood 1995;85:3144-9).

Investigators compared 25 healthy centenarians with two control groups of healthy people aged 18-50 years and 51-69 years. Each of these groups also was made up of 25 people.

The healthy centenarians showed laboratory signs of coagulation activation, including high levels of proteins that can predict cardiovascular disease in middle-aged people. Notably, the D-dimer concentrations were highly elevated in the centenarians: 323 ng/mL, compared with 29 ng/mL in the younger control group and 50 ng/mL in the middle group.

That healthy centenarians have significantly higher levels of D-dimer suggests that increased D-dimer "is not necessarily a bad thing. It is consistent with long life," Dr. Bauer commented.

While many coagulation activation markers increase with age, he focused on D-dimer because it has the potential to stratify recurrence risk in patients after treatment for their first idiopathic VTE and thereby identify who would benefit from extended anticoagulation.

Among several studies showing higher recurrence risk in patients with elevated D-dimer levels, he highlighted a multicenter investigation conducted in Italy (N. Engl. J. Med. 2006;355:1780-9).

In that study, D-dimer levels were tested 1 month after anticoagulation was stopped in patients who had a first unprovoked deep vein thrombosis or pulmonary embolism. Patients with normal levels did not resume therapy.

Those with "abnormal" D-dimer levels were randomly assigned to resuming or staying off treatment. Of the patients with elevated D-dimer levels, 74% were aged 65 years and older.

At a median follow-up of 1.4 years, 10.7% of untreated patients with abnormal D-dimer levels had a recurrence, compared with 4.4% of those with normal levels (hazard ratio 2.27).

When untreated patients were stratified by age, Dr. Bauer said the risk of recurrence was less in the elderly; they had a hazard ratio of 1.63, compared with 4.40 for those younger than age 65.

Among patients with normal D-dimer levels, however, he said recurrence was higher in the elderly.

In an interview immediately after the session, he cautioned against taking an alarmist stance when elderly patients present with high D-dimer levels.

"We are getting a lot of elderly referred because they have chronically elevated D-dimers with no history of thrombosis," he said. "One needs to be aware that [this is] probably something that goes along with age." ■

FDA Panel Offers Specifics for Revised CAP Trials

BY JAMIE HAMMON
"The Pink Sheet Daily"

Design of trials for community-acquired pneumonia drugs would face greater specificity but no major changes, according to recommendations from the Federal Drug Administration's Anti-Infective Drugs Advisory Committee.

The panel said at its April 2 meeting that a noninferiority margin of 10% in active-control noninferiority trials should be acceptable to prove efficacy of community-acquired pneumonia (CAP) drugs.

The FDA is working to update its guidance on CAP trial design and sought committee insight on how to translate the limited data from historic antibacterial trials into a scientifically verifiable treatment effect to serve as the basis for comparison to new antibiotics.

The committee discussed whether mortality data from CAP trials of penicillin, sulfonamides and tetracyclines in the early 1900s can serve to establish a treatment effect for comparator drugs on clinical outcomes and in different levels of disease severity.

Despite complications with data interpretation, the panel settled on the 10% noninferiority margin after unanimously agreeing that a treatment effect can be quantified for CAP studies of IV drugs in hospitalized patients, and they voted 10-3 that the same could be said for an oral formulation in outpatient CAP patients.

The discussion of CAP clinical trial design is part of the FDA's efforts to provide clearer guidance on antibiotic trial requirements.

Noninferiority trials are a popular option for anti-infectives, but the FDA has issued guidance requesting that superiority trials be conducted for several self-resolving community respiratory tract infections.

The FDA expressed concerns about use of noninferiority trials in CAP as well at a recent public workshop, noting that industry has provided the agency little data in support of the design. However, there is general consensus that conducting superiority or placebo-controlled trials in CAP patients is unrealistic. All clinical trials recently submitted to the FDA for a CAP indication have been noninferiority trials.

However, proper noninferiority trial design in CAP is challenging. The treatment effect for active comparators is unknown because no placebo-controlled trials have been conducted for CAP since the 1940s; and the conduct of further placebo-controlled trials is widely considered unethical due to the known value of antibiotics. The panel voted unanimously against placebo-controlled trials even for mild to moderate CAP.

Moreover, active comparator superiority studies are unattractive to industry due to the likelihood of failure to demonstrate superiority in the self-resolving condition, even for effective drugs.

Thus, development of new agents to treat CAP falls to active comparator noninferiority studies for which FDA is seeking to define an appropriate noninferiority margin and patient population.

ACCORDING TO THE PANEL, A NONINFERIORITY MARGIN OF 10% SHOULD BE ACCEPTABLE TO PROVE THE EFFICACY OF CAP DRUGS.

The original CAP trial draft guidance was issued in 1998. FDA has no timeline for completion of the updated policy, but said it is a priority.

In the meantime, the fate of several pending or planned CAP submissions await, including those for Advanced Life Science's cethromycin, Wyeth's tigecycline, Johnson & Johnson's ceftobiprole, and Forest Laboratories' ceftaroline.

"One of the realities of our work is that we often have to give guidance to individual companies in the absence of having updated officially the guidance," said John Jenkins, director of the FDA Office of New Drugs.

"If someone approaches us next week and says, 'we want to now discuss with you our program for CAP,' we'll do that. We probably won't directly apply the 1998 guidance. We won't be able to directly apply the future guidance. But we'll have to give them our best advice today, and what we heard from the committee informs what we will tell them today," he added.

There was some disagreement among the panel about how to extrapolate new end points from the treatment effect determined by the mortality in the historical data.

All of the committee members except one thought that it is fine to rely on the prior clinical data to evaluate mortality for CAP candidate drugs.

"We have far more patients with underlying conditions and comorbidities—it's very different right now from what it was in the 1930s. It's so difficult to interpret the data, I'm not sure we're doing anybody a favor by dealing with it," said one temporary voting member, Dr. Daniel Musher of Baylor College of Medicine.

The rest of the panel debated the appropriateness of evaluating measures of clinical efficacy for the new products.

Temporary voting member Dr. Thomas Fleming, University of Washington, argued that the extrapolation could not be statistically justified. "I think the fundamental principle that first needs to be recognized is that margins that you use are specific to end point. …Justifying the margin using data for one end point to another is conceivably possible but enormously complicated."

He urged that "mortality is still a highly clinically relevant end point, as well as one that historical data provide us the best sense as to what the effect of the active comparator is, given that's the base to do a valid noninferiority assessment."

"Sixty years ago, they didn't have any rescue medications," Jürgen Venitz, Medical College of Virginia, said, "so I do think there are other things that allow you to make that translation. I believe that we can translate quantitatively the mortality difference that they found 50-plus years ago to clinical success as we do it today."

The FDA seemed open to translating mortality data to support trials evaluating clinical outcomes. "It seems very reasonable to take what constitutes failure in the modern world and equate that with mortality," Office of Drug Evaluation Director Robert Temple said.

The panel agreed that a treatment effect can be quantified for noninferiority studies of oral formulations for outpatient CAP. There was general consensus that the same end points used for severe CAP could be used in testing for outpatient CAP drugs.

Those in favor of extrapolating the mortality data to the outpatient setting noted that modern medicine allows many patients that would have been hospitalized and placed on intravenous therapy at the time of the historical studies to be today treated as outpatients placed on oral antibiotics.

"I think everything we heard made us think that you continue to use that kind of end point here just as you would in the more severe illness," Mr. Temple said.

"What I heard is that people think that the data we have on severe illness is probably now applicable to people who aren't necessarily hospitalized because the modern world makes that unnecessary. But that really means they're fairly sick or have severe disease—we're not talking about things that you ordinarily think of as just really mild."

The panel also voted unanimously that establishing efficacy in severe CAP supports the drug's effect in less severe CAP, even though it has not been directly studied for that indication.

The panel also weighed in on how to determine disease severity. "The idea is to enrich for bacterial pneumonia," temporary voting member Scott Dowell, Centers for Disease Control and Prevention, said.

"The way you define CAP may be one of the most important things we do to enrich for those patients who actually have bacterial pneumonia," he noted.

"What seems reasonable and possible to do is you start out with a … clinical syndrome that looks very much like a typical bacterial pneumonia," said AstraZeneca Infection Clinical VP John Rex, the nonvoting industry representative.

"The classic syndrome needs to be an abrupt onset of a febrile syndrome that points to the chest, with a change on the chest x-ray, and probably with the ability to produce some sputum. Those things together suggest a bacterial etiology, and it's the acuity of the presentation," he said. ■

This publication and "The Pink Sheet Daily" are published by Elsevier.

Dr. Mark Metersky, FCCP, comments: *Sanity prevails at the FDA. While the desire for trials that prove that new antibiotics for CAP are better than currently available ones is understandable, the potential for lack of superiority and the prohibitive cost of such trials would likely dry up the pipeline of new antibiotics for CAP.*

Adjuvant Tx Reviewed

CT Screening • *from page 1*

The investigators concluded that screening for lung cancer can increase the rate of diagnosis and treatment, but might not meaningfully reduce the risk of advanced disease or death.

In place of routine screening, the guidelines committee recommended that high-risk individuals participate in a clinical trial evaluating CT screening.

If such a trial is not available, or if an individual is not eligible to participate in a trial, then he or she should go to a center of excellence with expertise in radiology, pathology, cytology, thoracic surgery, and general expertise in lung cancer treatment to discuss the potential risks and benefits before having a screening CT.

If the individual opts for screening, the committee recommended that the I-ELCAP screening protocol be followed.

In other updates, the committee decided to add a category 3 recommendation for use of adjuvant treatment of stage Ia NSCLC. "This indicates major disagreement among members as to which patients should get adjuvant therapy," commented Dr. Ettinger.

For stage IIIa disease with negative margins, the committee replaced a previous recommendation for chemoradiation followed by chemotherapy with a new recommendation for mediastinal radiation therapy.

In addition, surveillance recommendations for all NSCLC stages now include a chest CT every 4-6 months for 2 years in lieu of every 6 months. Again, this was a category 2B designation, indicating disagreement among panel members, Dr. Ettinger said.

The committee also designated cisplatin/etoposide and cisplatin/vinblastine chemotherapeutic regimens as preferred therapies. Paclitaxel/carboplatin was given a category 2B designation.

Dr. Ettinger disclosed the following affiliations and significant relationships: AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Co.; Eli Lilly & Co.; GlaxoSmithKline; Merck & Co.; MGI Pharma Inc.; Pfizer Inc.; and Sanofi-Aventis U.S. ■

Dr. Michael Alberts, FCCP, comments: *All hope that lung cancer screening by low-dose CT will be shown to provide a mortality benefit. Studies are underway that are designed to address this hypothesis.*

Until such information is available and because of the very real risks inherent in screening (e.g., false-positive results, unnecessary procedures, radiation exposure, psychological stress), the ACCP does not recommend screening outside the protections afforded by a clinical trial.

Diabetics Show Faster Decline in Forced Vital Capacity

BY KERRI WACHTER
Elsevier Global Medical News

Lung function declines more rapidly in diabetic individuals than in those without the disease, according to the results of a longitudinal, prospective analysis of more than 11,000 adults.

Over a 3-year period, individuals with diabetes had a decline in forced vital capacity (FVC) of 64 mL/year, compared with a decline of 58 mL/year in people without diabetes, a small but significant difference.

The decline in lung function has implications for clinical outcomes in elderly diabetics who develop respiratory or cardiovascular complications, wrote Hsin-Chieh Yeh, Ph.D., of the departments of epidemiology and medicine at Johns Hopkins University, Baltimore, and his colleagues (Diabetes Care 2008;31:741-6).

The researchers analyzed longitudinal data from the Atherosclerosis Risk in Communities (ARIC) Study—a community-based prospective cohort of 15,792 adults aged 45-64. The participants were recruited from North Carolina, Mississippi, Minnesota, and Maryland. The analysis included data from baseline to 3 years of follow-up. Those of ethnicity other than black or white were excluded. The researchers also excluded those in the upper or lower 1% of FVC, forced expiratory volume in 1 second (FEV_1), or FEV_1-to-FVC ratio at baseline or at 3-year follow-up, as these individuals were assumed to be outliers.

The final study sample included 11,262 subjects—1,100 with diabetes at baseline and 10,162 who were nondiabetic at baseline. At baseline and at the 3-year follow-up, FVC and FEV_1 were measured according to recommendations from the Epidemiology Standardization Project and the American Thoracic Society. Subjects were classified as having diabetes if they had a fasting glucose level of 126 mg/dL, had a nonfasting glucose level of at least 200 mg/dL, were currently using a diabetes medication, or answered positively to the question "Has a doctor ever told you that you had diabetes (sugar in the blood)?" Glycosylated hemoglobin A_{1c} levels were available for all 1,637 cases of prevalent type 2 diabetes at the second ARIC visit, as well as for a subgroup of 598 randomly selected nondiabetic individuals (from a previous study).

Compared with nondiabetic subjects, diabetics were more likely to be male, older, African American, and less physically active, and to have a greater body mass index and a higher waist-to-hip ratio. Diabetic subjects also had a greater prevalence of hypertension and higher white blood cell counts and fibrinogen levels.

Diabetics had significantly lower FVC, FEV_1, FVC% predicted, and FEV_1% predicted—by 133 mL, 72 mL, 3.6%, and 2.4%, respectively—than did nondiabetic subjects in cross-sectional analyses, after adjustment for age, gender, race, BMI, waist circumference, height, pack-years of smoking, sport activity index, educational level, and ARIC field center. These relationships were graded by fasting glucose, HbA_{1c} level, diabetes duration, and intensity of diabetes treatment, and were independent of traditional risk factors for lung function decline, such as age, smoking status, and central obesity.

Additional analysis showed that inflammatory markers—white blood cell count and plasma fibrinogen—attenuated the observed relationships only slightly.

In an accompanying editorial, Dr. Connie C.W. Hsia, FCCP, and Dr. Philip Raskin said that the study further advances the idea of the lung as a target of diabetic injury. "Think of the lung as a crime victim who unwittingly abets the perpetrator to hasten the demise of the host. Cumulative loss of pulmonary reserves eventually aggravates tissue hypoxia associated with any form of angiopathy in distant organs that ultimately underlies diabetic morbidity and mortality," wrote Dr. Hsia and Dr. Raskin, both of the internal medicine department at the University of Texas Southwestern Medical Center, Dallas (Diabetes Care 2008;31:828-9). ■

Dr. Nicola Hanania, FCCP, comments: *This study analyzed data from on a large prospective cohort study and compared lung function changes in diabetics and nondiabetics over 3 years. The authors conclude that diabetics have a faster decline in lung function parameters, especially FVC, compared with subjects without diabetes. This is an interesting observation that may explain the systemic comorbidities often seen in diabetics.*

Of note, the two cohorts compared were not age-, gender-, or race-matched, although correction for these confounding factors—as well as for differences in smoking status and body mass index—was done based on the authors' statements. Future studies will need to investigate the mechanism(s) of this difference in lung function decline. Systemic inflammation, which is common in diabetics with metabolic syndrome, may be the missing link for this observation.

Follow-Up Care Lacking for Lung Cancer Survivors

Survivors are at high risk for other primary cancers, cardiovascular disease, and osteoporosis.

BY FRAN LOWRY
Elsevier Global Medical News

HOLLYWOOD, FLA. — Cure rates for locally advanced lung cancer are increasing, but obtaining good follow-up care remains a challenge for the growing number of lung cancer survivors, Dr. Mark G. Kris, FCCP, told attendees at the annual conference of the National Comprehensive Cancer Network.

"Tens of thousands of people a year are leaving their surgeon's office and are told 'goodbye and good luck,' despite the fact that they've had a lung removed," said Dr. Kris, chief of the thoracic oncology service at Memorial Sloan-Kettering Cancer Center in New York.

"If you have cardiac bypass surgery, you can get Medicare to pay for your cardiac rehabilitation, but if somebody removes your lung, there is nothing," he said. "You walk out of your surgeon's office to your apartment or your home, and that's it. Hasta la vista, baby. It's time that changed."

Dr. Kris made follow-up care an issue during a presentation of updated National Comprehensive Cancer Network (NCCN) recommendations for the management of local and locally advanced non–small cell lung cancer (NSCLC). He attributed improved survivorship to advances in chemoradiation therapy and surgery.

"We have the ability to cure patients with advanced non–small cell lung cancer. There are tens of thousands of patients being cured of lung cancer every year, but [follow-up care] is something that is too often neglected. We need to keep this in mind," he said, listing areas that require long-term attention.

Because of their exposure to tobacco, NSCLC survivors are at very high risk—from 1% to 5% per year—for developing another primary cancer. As a result, Dr. Kris said, they need careful surveillance and should be asked about their smoking status. Indeed, he said he believes smoking status should be documented in the medical record at each follow-up office visit.

Survivors of lung cancer are also at risk for other smoking-related illnesses, such as chronic obstructive pulmonary disease and heart disease, he continued, and should be followed accordingly. In addition, radiation to the chest accelerates cardiovascular disease. As a result, lung cancer survivors need careful cardiac monitoring, including stress testing and lipid monitoring.

Radiation also accelerates osteoporosis, for which Dr. Kris said lung cancer survivors need to be prospectively treated, regardless of their general bone density, to protect against bone loss.

"These people have a lot of unmet needs. The time has come to pay attention to these needs," he said.

In his rundown of updates to the NCCN guidelines for local and locally advanced NSCLC, Dr. Kris noted the following on behalf of the guidelines committee:

- The standard of care remains anatomic resection, although ways of choosing lesser surgeries are currently an area of investigation. "To the surgeons in the audience, I know it doesn't make a lot of sense, when you have that one centimeter lump, to take out the entire right lower lobe, but that is still what we recommend."
- Whereas guidelines for other cancers stipulate a certain number of nodes to be sampled, in lung cancer, the recommendation covers the number of stations to be sampled.

"That number is three," Dr. Kris said.

- For stage IA NSCLC, the recommended treatment remains surgery. Adjuvant therapy is not recommended, but this negative recommendation was not unanimous: "It was a category 3 designation, so there was absolutely no agreement among the panel."
- The guidelines committee was in complete agreement on use of adjuvant cisplatin-based chemotherapy for completely resected patients with stages II and IIIA disease.
- It also gave a category 1 recommendation—its highest level of endorsement—for mediastinal radiation for IIIA disease.
- "The combination of cisplatin and vinorelbine is the most studied combination for adjuvant therapy for resected NSCLC and is the standard of care."
- The data are clear that adjuvant radiation has no benefit for clinically resected patients with stage I or stage II disease. Consensus among panel members was not as strong, however, regarding stage IIIA disease because of a lack of prospective level 1 evidence.

Dr. Kris disclosed that he is a consultant for Bayer HealthCare, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Co., Eli Lilly & Co. GlaxoSmithKline, Novartis Pharmaceuticals Corp., and Pfizer Inc. He receives grant and research support from sanofi-aventis U.S. ■

Salad Consumption May Influence Lung Cancer Risk

BY KERRI WACHTER
Elsevier Global Medical News

Eating at least four servings of salad vegetables per week is associated with a reduction in the risk of developing lung cancer in non-Hispanic whites, reported researchers at the University of Texas M.D. Anderson Cancer Center, Houston.

Compared with those who consumed four or more servings of salad per week, "those who consumed three or less than three servings per week actually have a two- to threefold increased risk of lung cancer among current smokers, former smokers, and never smokers," study investigator Michele Forman, Ph.D., a professor of epidemiology at the university, said at a press briefing. The briefing was held in conjunction with an annual conference on cancer prevention sponsored by the American Association for Cancer Research.

In a study that included more than 3,800 patients and controls, Dr. Forman and her colleagues recruited non-Hispanic white patients with lung cancer from the M.D. Anderson Cancer Center and matched them with non-Hispanic white healthy controls on the basis of age, gender, ethnicity, and smoking status.

Dietary data were obtained using a 129-item modified version of the National Cancer Institute/Block food frequency questionnaire. Responses were categorized according to the 2005 U.S. Department of Agriculture MyPyramid food guidelines. Participants also reported on physical activity levels throughout their adult years.

The researchers used models for current smokers, former smokers, and never smokers that were developed from an ongoing case-control study.

PEOPLE WHO ATE FEWER THAN FOUR SERVINGS OF SALAD PER WEEK HAD 2 TO 3 TIMES THE LUNG CANCER RISK OF THOSE WHO ATE MORE SERVINGS.

In particular, the researchers wanted to look at possible effects of fruit and vegetable consumption because "there has been a number of components in fruits and vegetables that has been associated with reduction in the risk of lung cancer in different populations," Dr. Forman said in an interview.

First, they added fruit consumption to the lung cancer risk prediction models for all three groups (current, former, and never smokers). Fruit intake had no effect on lung cancer risk for any of the groups.

Next, they looked at vegetables. Salad vegetables included carrots, lettuce, onions, and others, the consumption of which individually is a predictor of lung cancer risk. The researchers also adjusted for factors that could affect diet, such as socioeconomic factors and age.

They found that among never smokers, those who consumed three servings of salad per week had a more than twofold increased risk (odds ratio 2.09) of developing lung cancer, compared with those who consumed four or more servings per week. In the same group, those who consumed fewer than three servings per week had a slightly higher risk of developing lung cancer (OR 2.15). The results were similar for former smokers.

Among current smokers, those who ate three or fewer servings of salad per week had an almost threefold increased risk of lung cancer (OR 2.73), compared with smokers who ate four or more salad servings per week.

There was little physical activity reported among those with lung cancer, Dr. Forman said. However, gardening was reported in both healthy controls and those with lung cancer.

The researchers found that among current, former, and never smokers, gardening at least once a week was associated with a 30%-40% reduction in lung cancer risk.

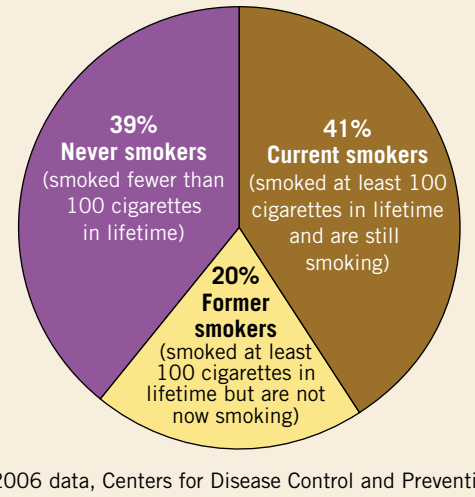
Among never smokers, those who worked in the garden once or twice a week had a 40%-46% lower risk of lung cancer, compared with those who did not report any gardening. Results were similar for former smokers. Among current smokers, gardening once or twice per week was associated with a 33%-45% reduction in risk.

"Now, gardening is a funny physical activity. It could be [anything from] cutting flowers to planting a tree," Dr. Forman said. The activity questionnaires did not provide enough detail to determine what respondents meant by "gardening." Despite this range of exertion, one common element to all gardening activities is sun exposure and, therefore, vitamin D exposure.

"These are very preliminary findings," Dr. Forman said. The researchers are planning to look more closely at the data to determine if their study population was a selective subset of individuals with a healthier lifestyle in general. ■

DATA WATCH

More Than Half of Chronic Bronchitis Patients Are Current or Former Smokers



Source: 2006 data, Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS

Hospitals Tackle New Joint Commission Safety Goal

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

The Joint Commission's new 2008 patient safety goal of requiring a process to respond quickly to a deteriorating patient is being mistakenly interpreted at some hospitals as a mandate for "rapid response teams" or "medical emergency teams."

Further, at some organizations that already have rapid response teams, staff have expressed concerns they will need to redo their established systems.

Dr. Peter Angood, vice president and chief patient safety officer for the Joint Commission, said such presumptions are incorrect.

Hospitals are simply being asked to select a "suitable method" that allows staff members to directly request assistance from a specially trained individual or individuals when a patient's condition appears to be worsening, he said. The key is to focus on early recognition of a deteriorating patient and mobilization of resources and to document the success or failure of the system that is in place. "This is not a goal that states there needs to be a rapid response team," Dr. Angood said.

Many institutions in the United States have implemented rapid response teams, and the data on their efficiency are generally good, but not every study has been positive, Dr. Angood said. As a result, officials at the Joint Commission wanted to move forward with a more basic approach with the goal of avoiding variation in response from day to day and from shift to shift. (See sidebar.)

Regardless of how hospitals choose to implement the Joint Commission's goal, hospitalists are likely to play a significant role in accomplishing it, said Dr. Franklin Michota, director of academic affairs for the department of hospital medicine at the Cleveland Clinic.

Organizations that already have hospitalist programs in place are leaning toward the use of rapid response teams or medical emergency teams, because hospitalists can function as members of the team. Some hospitals without an adequate number of staff to have a team in place around the clock are considering starting hospitalist programs. Another strategy would be to form teams that do not include physicians, he said.

The Joint Commission's requirement will not be without cost, Dr. Michota said, especially for those organizations that need to add staff. If no professional staff was there at 2 a.m. before, the hospital now needs to take on the cost of salary and benefits for more employees, he said.

ELIZABETH ZHANI/THE JOINT COMMISSION

The key is to focus on early recognition of a deteriorating patient and mobilization of resources, Dr. Peter Angood said.

When hospitalists aren't a part of a response team, they are likely to be central to developing the response plan, said Dr. Robert Wachter, chief of the division of hospital medicine at the University of California, San Francisco. And perhaps the biggest role for the hospitalist is in providing the around-the-clock coverage that could negate the need to call the formal response team as often, he said.

While the Joint Commission's requirement might seem like a greater challenge for small hospitals, Brock Slabach, senior vice president for member services at the National Rural Health Association, disagrees. In many cases, smaller organizations can meet the Joint Commission's requirement in easier fashion than large, urban facilities can, because they are more nimble and can work faster with less bureaucracy.

Rapid response teams, for example, can be tailored to a hospital's resources by using staff from the emergency department to respond to a call, he said.

A number of hospitals have already made a commitment to establishing some type of rapid response teams. Establishing these teams is one of the strategies advocated as part of the Institute for Healthcare Improvement's 5 Million Lives Campaign, a national patient safety campaign designed to reduce harm in U.S. hospitals.

Of the 3,800 hospitals enrolled in the 5 Million Lives Campaign as of January, about 2,700 have committed to using rapid response teams, according to IHI.

This idea is catching on, said Kathy Duncan, R.N., faculty for the 5 Million Lives Campaign.

The cost of implementing these types of teams varies, she said. About 75% of hospitals in the campaign have done this with zero increase in full-time employees, she said. For most staff involved, this is just an additional task. Investment is required for training team members, which can be costly at the outset, she said. Hospitals also need to invest time to educate the rest of the staff on when and how to call for assistance.

Ms. Duncan's advice for implementing whatever process hospitals choose to respond to the Joint Commission's goal is to start by assessing what resources are available. Next, don't just jump into implementation, but take the time to test the process and figure out how people will request assistance, when to make that call, and who should respond. "Start small with a pilot process," Ms. Duncan said. ■

Implementing a Response Plan

Because of the complexity of implementing a process to respond quickly to a deteriorating patient, officials at the Joint Commission are giving hospitals a year to develop and phase in their program.

By April 1, the first deadline, hospital leaders were required to assign responsibility for the oversight, coordination, and development of the goals and requirements. By July 1, there needs to be an implementation work plan in place that identifies the resources needed. By Oct. 1, pilot testing in one clinical area should be underway.

The Joint Commission is serious about organizations meeting these implementation milestones, Dr. Angood said. Hospitals that don't meet the quarterly deadlines will be docked points on their evaluation.

For 2009, hospitals will need to comply with the following six "implementation expectations" set out by the Joint Commission:

- Select an early recognition and response method suitable to the hospital's needs and resources.
- Develop criteria for how and when to request additional assistance to respond to a change in a patient's condition.
- Empower staff, patients, and/or families to request additional assistance if they have a concern.
- Provide formal education about response policies and practices for both those who might respond and those who might request assistance.
- Measure the utility and effectiveness of the interventions.
- Measure cardiopulmonary arrest rates, respiratory arrest rates, and mortality rates before and after implementation of the program.

Shock Index and Age Improved Prediction of Mortality

BY ROBERT FINN
Elsevier Global Medical News

HUNTINGTON BEACH, CALIF. — In patients older than 55 years, multiplying a patient's age by the Shock Index—a ratio of heart rate to systolic blood pressure—provides a better predictor of 48-hour mortality than using the Shock Index alone, Dr. Ben L. Zarzaur said at the Academic Surgical Congress.

The Shock Index (SI) has long been known to provide a better predictive rule of thumb than heart rate or blood pressure alone, Dr. Zarzaur said. Better still are several measures such as the Injury Severity Score, the Revised Trauma Score, and the Trauma Injury Severity Score—but they use relatively complex equations and can be difficult to calculate in the resuscitation room.

In contrast, the Shock Index is simple to calculate but does not take into account the effect of patient age.

Dr. Zarzaur of the Presley Memorial Trauma Center at the University of Tennessee, Memphis, and his colleagues conducted a retrospective cohort study that involved a total of 16,077 patients, aged 18-81 years, who were admitted to the trauma center between 1996 and 2005. All were victims of blunt trauma, and all arrived with a palpable pulse of at least 10 beats per minute and a systolic blood pressure of at least 30 mm Hg.

The investigators excluded victims of neurotrauma, those who were admitted more than 24 hours after the injury, and those whose records lacked data on pulse rate and blood pressure.

WHEN THE PRODUCT OF AGE TIMES SHOCK INDEX WAS AT LEAST 50, IT PREDICTED SIGNIFICANT EARLY MORTALITY IN PATIENTS OLDER THAN 55 YEARS.

They divided the patients into two groups: those who were 55 years old or younger and those older than 55 years. The mean age of the younger patients was 34 years and that of the older patients was 67 years.

The primary outcome measure was death within 48 hours, and the investigators used the need for a blood transfusion during that time period as a secondary outcome.

They performed an analysis of the area under the receiver operating curves (ROC), a statistical method that quantifies the balance between sensitivity and specificity, to determine which measures were best.

Among the younger patients, SI alone had a significantly larger ROC area than did pulse rate, systolic blood pressure, or age multiplied by SI. An SI score greater than 0.8 successfully predicted significant early mortality and transfusion in this age group.

In the older patients, on the other hand, age multiplied by SI had a larger ROC area than did the other measures. When age was multiplied by SI, a resulting product that was 50 or greater successfully predicted significant early mortality and transfusion in the older patients.

Dr. Zarzaur declared that he had no financial conflicts related to the study. ■

Universal MRSA Screening Slashed Rates by Half

Treatment of patients who tested positive decreased prevalence of four types of MRSA.

BY HEIDI SPLETE
Elsevier Global Medical News

Rates of methicillin-resistant *Staphylococcus aureus* infections were reduced by more than half when all newly admitted hospital patients were tested for MRSA, according to results from three hospitals.

Methicillin-resistant *S. aureus* (MRSA) has become a fixture in many hospitals in the United States, and the resulting MRSA infections are causing poor health outcomes and increasing health care costs, reported Dr. Ari Robicsek of Evanston (Ill.) Northwestern Healthcare and his colleagues.

To cut MRSA infection rates, the researchers implemented a universal MRSA surveillance program at a three-hospital organization in Chicago.

Their observational study compared MRSA rates during a baseline year when patients were not universally screened at the time of hospital admission with MRSA rates after conducting polymerase chain reaction–based nasal tests for MRSA. The tests were conducted for 1 year on all patients who were admitted to the intensive care unit and for another year on all patients admitted to the hospital (Ann. Intern. Med. 2008;148: 409-18).

During the ICU surveillance year, 3,334 of 4,392 patients (76%) admitted to the ICU were tested for MRSA and 277 (8%) were positive. During the universal screening year, 62,035 of 73,464 patients (84%) admitted to the hospital were tested for MRSA and 3,926 (6%) were positive. Patients who tested positive were isolated. Of the 2,085 patients for whom mupirocin data were available, a total of 1,288 (62%) received at least four doses of mupirocin.

During the year of universal surveillance, the total number of isolation days was 11,454 across the three hospitals. "With no surveillance, clinical cultures alone would have captured 2,036 of those days," the investigators noted.

"Thus, 9,418 MRSA patient-days would have been spent without infection control contact precautions to limit MRSA spread."

Overall, the prevalence density of clinical infections caused by MRSA decreased from 8.9/10,000 patient-days during the baseline year to 7.4/10,000 patient-days during the ICU screening year, but this difference was not statistically significant. By contrast, prevalence density decreased significantly from baseline to 3.9/10,000 patient-days during the universal screening year.

In addition, the prevalence density of four types of MRSA infections—bloodstream, respiratory tract, urinary tract, and surgical site infections—dropped significantly between baseline and the end of the universal screening year.

This improvement in MRSA rates following universal screening persisted for up to 30 days after the patients left the hospital but had no apparent effect on infection rates from 31 days to 180 days. The types of infections represented the major body sites that might be affected by culture-confirmed MRSA, the researchers noted.

To control for a possible unrecognized coinfection, the researchers also compared changes in rates of hospital-associated MRSA bacteremia with rates of hospital-associated methicillin-susceptible *S. aureus* (MSSA) bacteremia. The MRSA bacteremia rates decreased significantly after the surveillance program was implemented, but the MSSA bacteremia rates did not.

The study was limited by the lack of an unscreened control group and the inclusion of only one hospital organization, but the findings support results from previous investigations in which anything less than universal screening detected fewer than 20% of patients with MRSA infections.

"However, given the intermediate size and community-based nature of our three hospitals, our experience is probably representative of most U.S. hospitals," the investigators wrote.

The impact of decolonization on MRSA control was not measured in this study and is an area deserving further research, they noted.

But using the same MRSA screening strategy for every hospital may not be feasible.

In an accompanying editorial, Dr. Ebbing Lautenbach of the University of Pennsylvania, Philadelphia, observed that commitment and support of each hospital's administration is needed for universal MRSA screening to succeed and that the cost of rapid screening tests may be a barrier for some facilities (Ann. Intern. Med. 2008;148:474-6).

"As each institution continues to refine its own plan to address MRSA, we need better evidence to point us toward what works best in the complex universe of MRSA screening," he said. ■

BiLE Tops Other Liver Transplant Scoring Methods

BY ROBERT FINN
Elsevier Global Medical News

A scoring method that combines bilirubin and lactate values with the specific etiology of acute liver failure better predicts death or the need for transplant than do existing methods, Dr. Johannes Hadem and colleagues reported in an article appearing in the March 2008 issue of Clinical Gastroenterology and Hepatology.

The new scoring method, known as the bilirubin-lactate-etiology (BiLE) measure, has a sensitivity of 79% and a specificity of 84% for predicting death or the need for transplant if the patient's score is greater than 6.9.

These sensitivity and specificity values are significantly better than are other measures including the Model for End-Stage Liver Disease (MELD) and the Simplified Acute Physiology Score III (SAPS-III), according to Dr. Hadem of Hannover (Germany) Medical School, and his colleagues.

The BiLE score is simple to calculate and is especially suited to bedside use immediately after admission to the intensive care unit, wrote the investigators.

But because of the diversity of acute liver failure etiologies in different regions of the world, the BiLE score will need to be validated in other centers and with other patient cohorts.

In order to develop the BiLE score, the investigators conducted a retrospective analysis of 102 patients from the intensive care unit of a single institution who fulfilled the diagnostic criteria for acute liver failure.

Of those patients, a total of 39 survived for a period of at least 8 weeks without the need for orthotopic liver transplant (OLT), 18 died without OLT, 5 died following OLT, and 40 survived following OLT. In all, 79 of the patients (77%) survived to week 8.

THE BILE SCORE ACHIEVED A SENSITIVITY OF 79% AND A SPECIFICITY OF 84% FOR PREDICTING DEATH OR THE NEED FOR TRANSPLANT.

For the purposes of the study, patients who had hepatic dysfunction were diagnosed with acute liver failure if they had hepatic encephalopathy, acute-onset increase of the international normalized ratio (INR) greater than 1.5, and the absence of signs of chronic liver disease during the clinical and the ultrasound examinations.

The investigators did not find any predominant etiology for acute liver failure among the patients in the study. Cryptogenic acute liver failure was the etiology in 21 patients, acute hepatitis B in 18, acetaminophen ingestion in 16, Budd-Chiari syndrome in 9, phenprocoumon toxicity in 7, idiosyncratic drug reactions in 5, *Amanita phalloides* ingestion in 5, Wilson's disease in 5, hepatitis A in 4, ischemic hepatitis in 4, and halothane reaction in 3. The remaining 5 patients had etiologies classified as "other."

In comparing patients who survived with those who died or required a liver transplant, the investigators found that 15 different laboratory values and other characteristics showed statistically significant differences.

Multivariate linear regression revealed that bilirubin and lactate levels were the most predictive of survival. Patients who survived without undergoing transplantation had a mean bilirubin level of 103 micromol/L, compared with 263 micromol/L in the liver transplantation or death group.

Similarly, patients who survived without transplantation had a mean lactate level of 2.9 mmol/L, compared with a mean value of 4.7 mmol/L in the liver transplantation or death group.

There were significant differences between the groups in etiology as well. Patients with cryptogenic acute liver failure, Budd-Chiari syndrome, or phenprocoumon toxicity were more likely to die or require transplantation, while those with acetaminophen toxicity were more likely to survive without the need for transplantation.

The investigators designed the BiLE score empirically. In order to bring bilirubin and lactate into the same range of values, the equation calls for dividing bilirubin concentrations in micromol/L by 100. To this figure, one adds the lactate concentration in mmol/L and then adds or subtracts a value depending on the etiology (see sidebar).

Using a cutoff value of 6.9 to predict death or the need for transplantation, the investigators found that the BiLE score achieved a sensitivity of 79%, a specificity of 84%, a positive predictive value of 89%, and a negative predictive value of 71%.

The sensitivity of the BiLE score was 100% in patients with cryptogenic acute liver failure.

In contrast, using the value of lactate alone with a cutoff of 3.5 mmol/L achieved a sensitivity and specificity of 59% and 66%, respectively.

The MELD score with a cutoff of 32 achieved a sensitivity and specificity of 65% and 69%, respectively, while the King's College Criteria achieved a sensitivity and specificity of 58% and 82%, respectively.

The investigators stated that they had no conflicts of interest to report. ■

Calculating the BiLE Score

The calculation method for the BiLE score is as follows:

Bilirubin (micromol/L)/100 + lactate (mmol/L)
+ 4 (in the case of cryptogenic acute liver failure, Budd-Chiari syndrome, or phenprocoumon toxicity)
– 2 (in the case of acetaminophen toxicity)
+ 0 (in the case of other etiologies)

BiLE scores above 6.9 are predictive of death or liver transplantation.

Pages 8a—8b

Glucose Control May Lower Infections in Burn Injuries

Maximum blood glucose above 140 mg/dL predicted infection with 91% sensitivity, 62% specificity.

BY JEFF EVANS
Elsevier Global Medical News

CINCINNATI — Control of blood glucose levels through intensive insulin therapy has been shown to reduce morbidity both in surgical and medical ICU patients, as well as mortality in surgical ICU patients. Results of a retrospective study now suggest that implementation of this therapy in burn patients may reduce the rate of infectious complications but not mortality.

Maintaining mean blood glucose levels of less than 140 mg/dL reduced the rate of pneumonia, ventilator-associated pneumonia, and urinary tract infections in 71 burn patients who received intensive insulin therapy, compared with 81 burn patients in the same ICU during the year before the protocol was implemented, Dr. Mark R. Hemmila reported at the annual meeting of the Central Surgical Association.

Intensive insulin therapy significantly reduced rates of pneumonia overall (16% vs. 37%).
DR. HEMMILA

But some discussants at the meeting questioned whether certain weaknesses in the study's design and differences in patient characteristics may have contributed to its results.

During the first year of an intensive insulin therapy protocol (July 2005 to June 2006), Dr. Hemmila and his colleagues at the University of Michigan, Ann Arbor, sought to bring burn patients' blood glucose levels to less than 140 mg/dL. In the previous year (July 2004 to June 2005), burn patients had received an insulin drip protocol when their blood glucose levels exceeded 150 mg/dL.

The patients in each group had a mean age in the early 40s, and close to three-fourths in each group were men. The investigators excluded patients with concomitant trauma and burn injuries or desquamating skin diseases.

The control and intensive insulin therapy groups had similar blood glucose levels upon admission (142 mg/dL vs. 130 mg/dL, respectively) and in terms of daily average (135 mg/dL vs. 129 mg/dL) as well as overall mean during their hospital stay (127 mg/dL vs. 126 mg/dL). The intensive insulin-treated and control groups each spent a similar percentage of time in the hospital with a mean daily blood glucose level greater than 140 mg/dL (22% vs. 35%, respectively). But compared with patients in the control group, those who were treated with intensive insulin therapy spent a significantly lower percentage of their time in the hospital with a maximum mean daily blood glucose level greater than 200 mg/dL (11% vs. 17%).

In multivariate analyses that adjusted for age, gender, the percentage of total body surface area burned, and inhalation injury, adding intensive insulin therapy did not significantly improve the outcomes obtained in burn patients in the year before the therapy was implemented. There were no improvements in mortality (7% vs. 9%, respectively, among intensive insulin vs. control patients), mean length of stay in the ICU (5 vs. 9 days), mean length of stay in the hospital overall (10 vs. 17 days), and mean number of days requiring ventilation (3 vs. 6 days).

However, intensive insulin therapy significantly reduced rates of pneumonia overall (16% vs. 37%), ventilator-associated pneumonia (10% vs. 31%), and urinary tract infection (6% vs. 22%).

The odds of developing infection were more than 11 times higher in patients with a maximum mean glucose of greater than 140 mg/dL than in those with a maximum blood glucose level of 140 mg/dL or less. Of patients with maximum blood glucose levels higher than 140 mg/dL, 61 had an infection and 32 did not, whereas those with blood glucose levels of 140 mg/dL comprised 6 with infection and 53 without. Based on these values, a maximum blood glucose level greater than 140 mg/dL predicted the development of infectious complications with 91% sensitivity and 62% specificity, Dr. Hemmila said.

"Measurement of a blood glucose level greater than 140 mg/dL should heighten the clinical suspicion for presence of an infection in patients with burn injury," he concluded.

Dr. Peter J. Fabri of the University of South Florida, Tampa, a discussant at the meeting, noted a recent study suggesting that the complication rate of tight blood glucose control may actually negate its benefits (N. Engl. J. Med. 2008;358:125-39). "We have to be very careful being critical when we look at these studies," Dr. Fabri said. "It's very rare that one thing is the only thing that changes in a busy, successful critical care unit over a 2-year period of time."

Dr. Fabri pointed out that the median length of stay was 4 days in the intensive insulin group and 12 days in the control group. "This suggests that there may, in fact, be other changes that are going on getting patients out of the unit quicker," he said.

He also noted that the control group had a (nonsignificant) higher incidence of inhalation injury than did the intensive insulin–treated group (37% vs. 31%), as well as a higher rate of second- and third-degree burns. Dr. Hemmila said that he was not aware of any particular ICU protocol changes that were made during the study period.

Other discussants commented that the average total body surface area of the burns was small (19% in controls and 15% in intensive insulin–treated patients).

Dr. Hemmila and some of the discussants noted that the "chicken or the egg" question of what came first—hyperglycemia or infection—is still unresolved. ■

Hyperglycemia Poses Risks In Acute Coronary Syndrome

BY ROBERT FINN
Elsevier Global Medical News

Hyperglycemia is common in acute coronary syndrome and is a strong predictor of poor outcome, but many questions remain about how to take these facts into account in clinical practice, according to a scientific statement from the American Heart Association.

Although it's still uncertain whether treating hyperglycemia in acute coronary syndrome (ACS) produces definite benefits, it's reasonable to consider intensive glucose control in patients with plasma glucose levels above 180 mg/dL, and even for some patients with milder degrees of hyperglycemia, according to the members of the writing group, which was led by Dr. Prakash Deedwania of the University of California, San Francisco (Circulation 2008 Feb. 25 [doi:10.1161/circulationaha.107.188629]).

"Most cardiologists are not aware of the importance of hyperglycemia in the acute coronary syndrome," Dr. Deedwania said in an interview.

More than 2 million patients are treated in the United States annually for ACS, and as many as 50% of them might have hyperglycemia, Dr. Deedwania said. Numerous analyses and meta-analyses have found increased risks associated with hyperglycemia in ACS. The largest retrospective study, which involved 141,680 patients, found that hyperglycemia increased the risk of 30-day mortality by 13%-77%, and it increased 1-year mortality by 7%-46%, depending on the degree of hyperglycemia.

The risks appear to be greatest in hyperglycemic patients with no previous evidence of diabetes, but it's still unclear whether hyperglycemia is a marker or a mediator of adverse outcomes.

The most pressing unanswered question, according to Dr. Deedwania, is to determine which treatment for hyperglycemia has the best combination of efficacy and safety. One large recent trial demonstrated that hypoglycemia can be more dangerous than hyperglycemia, so it's important to figure out how critical it is to control hyperglycemia and to what extent it should be controlled.

Other important areas in need of further investigation include whether persistent hyperglycemia during ACS hospitalization has a greater impact on prognosis than does admission hyperglycemia alone, whether there is a critical period of vulnerability from hyperglycemia in these patients, whether the best target glucose levels differ in patients with and without preexisting diabetes, and what the optimal timing of therapy might be.

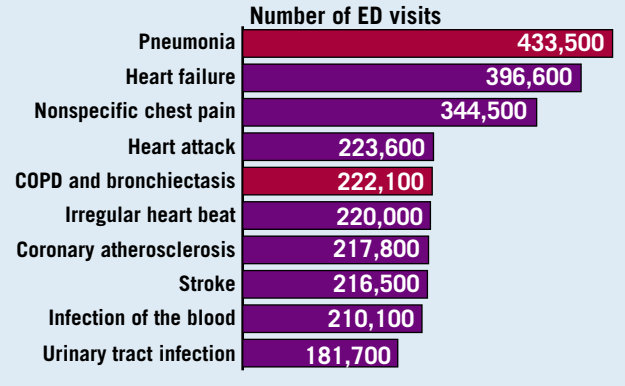
Meanwhile, the writing group determined that there is excellent (level A) evidence available today to recommend that glucose levels should be part of the initial laboratory evaluation in all patients with suspected or confirmed ACS. And there is good (level B) evidence that glucose levels should be monitored closely in patients with ACS admitted to an ICU, that it's reasonable to consider treatment in patients with high levels of hyperglycemia, that insulin by intravenous infusion is the most effective measure to control glucose in ICU patients, and that special attention should be paid to ACS patients with hyperglycemia but no prior history of diabetes.

The evidence is somewhat weaker (level C) for several other recommendations. For example, efforts to optimize glucose control may be considered in patients with milder hyperglycemia, and normoglycemia (plasma glucose between 90 and 140 mg/dL) appears to be a reasonable goal for treatment.

In addition to informing physicians about the importance of hyperglycemia in ACS, the release of the American Heart Association's scientific statement has another goal, Dr. Deedwania said. "This is a call to action for all the different agencies, such as the National Institutes of Health, to consider doing trials on some of these very specific questions. This should be a priority." ■

DATA WATCH

Top 10 Emergency Department Diagnoses Resulting in Hospital Stays



Note: Based on the principal diagnosis on the inpatient record for 23 states in 2005.
Source: Healthcare Cost and Utilization Project

ELSEVIER GLOBAL MEDICAL NEWS

Preemie Asthma Tied to Mom's Chorioamnionitis

BY MITCHEL L. ZOLER
Elsevier Global Medical News

PHILADELPHIA — Children born prematurely to mothers who developed chorioamnionitis during pregnancy were about fourfold more likely to develop asthma and wheezing during the first 2 years of life, compared with term infants born to mothers without chorioamnionitis, based on data collected on nearly 1,100 children.

What was surprising was the degree of the association with wheezing and asthma.
DR. KUMAR

The finding needs to be extended by following the children to an older age and by studying other populations. If the findings are confirmed in such studies, earlier treatment and resolution of chorioamnionitis may have important implications for the future respiratory health of affected children, Dr. Rajesh Kumar said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

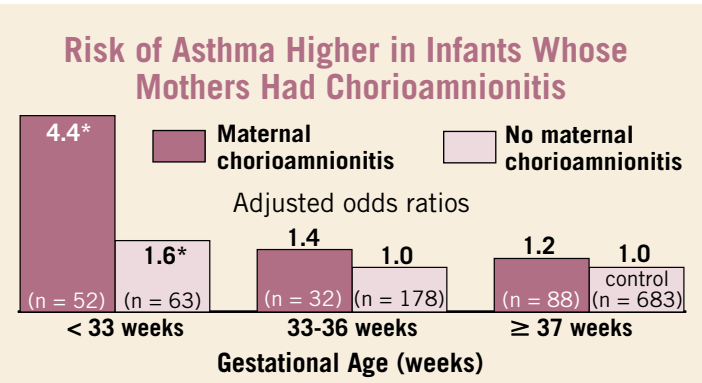
"A lot of the chorioamnionitis was subclinical. We don't know if treatment will prevent the effect of chorioamnionitis on recurrent wheezing, but this would be an area for future study," Dr. Kumar said in an interview.

"What was surprising was the degree of association that chorioamnionitis had with wheezing and asthma," whereas no link was seen between prematurity, chorioamnionitis, and food allergy or eczema, said Dr. Kumar, a pediatric allergy and asthma specialist at Children's Memorial Hospital and Northwestern University, both in Chicago. Atopy does not appear to play a role in the association.

An alternative, physiological explanation is that chorioamnionitis produces a strong, proinflammatory response that boosts levels of various cytokines, such as tumor necrosis factor–α, and interleukin-6 and -8. Cytokines like these may trigger premature birth, and may also lead to chronic respiratory disease in the fetus.

Results from some prior studies had shown a link between prematurity and an increased risk for asthma, but this link was not confirmed in all studies. Prior studies did not consider the underlying pathogenesis that led to premature birth, which may account for the inconsistency, Dr. Kumar said.

His analysis was based on data from children in the Boston Birth Cohort, an ongoing study at Boston Medical Center that began in 1998. Included were 771 term and 325 preterm infants who completed at least one postnatal examination. These numbers make the analysis one of the few prospective studies large enough to allow stratification of the infants in groups according to the severity of prematurity and the presence of chorioamnionitis, he noted. The average age of the children at their last follow-up visit was 2.2 years.



*Statistically significant.
Notes: Based on an average 2.2-year follow-up. Adjusted for factors including infants' age, breast-feeding, and postnatal passive smoking.
Source: Dr. Kumar

ELSEVIER GLOBAL MEDICAL NEWS

The analysis adjusted for several infant and maternal variables, including breast-feeding, postnatal passive smoking, maternal smoking during pregnancy, and maternal educational status. Infants born at less than 33 weeks' gestation to mothers who had chorioamnionitis were 4.0-fold more likely to wheeze and 4.4-fold more likely to have asthma, compared with infants born at 37 weeks or beyond to mothers without chorioamnionitis. (See box.) Both differences were highly significant.

In contrast, infants born before 33 weeks to mothers without chorioamnionitis were 2.7-fold more likely to wheeze (a significant difference) but were no more likely to have asthma than were term infants.

"One of the major issues in our study was that our primary outcome was recurrent wheezing of early childhood. We also evaluated physician-diagnosed asthma, but this is a bit less clear of a diagnosis at a young age. We will continue to follow these children [until] they are 6 years of age to see if the effects of chorioamnionitis on physician-diagnosed asthma will truly equate to persistent asthma by the time the children are older," Dr. Kumar said.

The associations were even stronger in infants born to African American mothers, who made up about 62% of the study cohort. ■

Asthmatic Children Bear the Brunt of the Influenza Burden

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

The influenza-related hospitalization rates for young children with asthma were four times greater than those of children without asthma, and outpatient visits attributable to influenza were about twice as likely among those with asthma, according to Dr. E. Kathryn Miller and her associates.

The results are similar to those of reviews that found that the rate of influenza-attributable outpatient visits for children with asthma and other medical conditions was higher than among healthy children, the investigators noted. But they added that their study may be the first to use prospective, laboratory-confirmed surveillance over several years to estimate rates of influenza-attributable visits for these two groups of children (Pediatrics 2008;121:1-8).

The investigators conducted a prospective study that included children aged 6-59 months. Patients were either hospitalized between 2000 and 2004 or presented to clinics or emergency departments with acute respiratory illnesses (ARIs) or fever during two flu seasons between 2002 and 2004. In both the hospital and outpatient settings, throat and nasal swabs were obtained and tested for influenza, said Dr. Miller of the department of pediatrics at Vanderbilt University in Nashville, Tenn.

Of the 1,468 children hospitalized, 81 (6%) had lab-confirmed influenza; about one-quarter of these 81 children had asthma. Among children aged 6-23 months, the average annual rate of hospitalizations attributable to influenza was 2.8 cases/1,000 children with asthma, compared with 0.6 cases/1,000 children among healthy children, a significant difference. But the difference was not significant among those children aged 24-59 months: 0.6 cases/1,000 children among those with asthma, vs. 0.2 cases/1,000 children among the healthy children.

Among the 1,432 children enrolled in the outpatient settings, influenza was confirmed in 249 patients (17%); 15% had asthma. Among the children aged 6-23 months with asthma, the average annual rate of outpatient visits attributable to influenza was 316/1,000 children, compared with 152/1,000 children among healthy children. Among those children aged 24-59 months, the rates were 188 cases/1,000 children with asthma, vs. 102 cases/1,000 healthy children in 2003-2004. Both differences were statistically significant.

Vaccination rates were 27% in the asthma group and 12%-15% in children without asthma, according to parent reports. ■

Necrotizing Pneumonia on the Rise in Children

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. — More children with pneumonia are developing necrotizing pneumonia from a growing variety of infectious agents, including methicillin-resistant *Staphylococcus aureus*, according to a retrospective, 15-year study.

"Necrotizing pneumonia is real," Dr. Andrew Colin said. If a child has a persistent fever that does not respond to treatment for 3 or more weeks, along with pleural effusions suggesting community-acquired pneumonia, consider coexisting necrotizing pneumonia, he said.

Multiple organisms are playing a role, "including a lot of necrotizing pneumonias where we do not know the organism. These could be mycoplasma," said Dr. Colin, director of the division of pediatric pulmonology, Holtz Children's Hospital at the University of Miami/Jackson Memorial Medical Center in Florida.

Of 80 patients, a total of 38 (48%) had positive cultures. *Streptococcus pneumoniae* was the predominant organism, although in the more recent years there was a variety of organisms responsible, most notably methicillin-resistant *Staphylococcus aureus* (MRSA), Dr. Colin said at a pediatric pulmonology meeting sponsored by the American College of Chest Physicians.

Dr. Colin, along with Dr. Gregory Sawicki (the study's lead author) and associates, found an increasing incidence of necrotizing pneumonia from January 1990 to February 2005 at Children's Hospital Boston (Eur. Respir. J. 2008 Jan. 23 [Epub ahead of print]). Of 80 cases identified, there was 1 case during 1993-1994; 11 each during 1995-1996 and 1997-1998; 17 cases during 1999-2000; and 12 cases during 2001-2002.

"By the end of the study, years 2003-2004, we had 28 cases in one hospital, which is quite significant," Dr. Colin said.

A meeting attendee asked if children at greater risk for necrotizing pneumonia can be identified.

"We don't have large enough numbers to predict who will develop necrotizing pneumonia," responded Dr. Colin, who is also professor of pediatrics at the University of Miami.

Necrotizing pneumonia presents with coexisting effusion in a majority of patients. In the study, 69 children (86%) had pleural effusion with a low pH (mean 7.08).

It is clinically challenging to differentiate the signs and symptoms of necrotizing pneumonia from the effusion, Dr. Colin said.

Computed tomography with contrast is the best way to diagnose necrotizing pneumonia, Dr. Colin said. The imaging detects the characteristic features, the liquefaction and cavitation of lung tissue. Look for demarcation between lung and liquid lung, he suggested.

How to differentiate a lung abscess from liquid in the lung on the imaging was another meeting attendee question. "The differential diagnosis is absolutely critical," Dr. Colin said. On the CT scan, abscesses appear with thick walls, whereas necrotizing lungs have thin walls and will collapse in a couple of days, he replied. Also, "if you tap the two, the abscess will be positive in culture, the necrotizing lung will be negative." Although the lungs are often sterile with necrotizing pneumonia, "there are some bad bugs, so everyone gives antibiotics just in case."

Dr. Colin advocated a conservative approach to prolonged chest tube drainage in patients who develop necrotizing pneumonia. In another of his studies, five of nine children with the condition developed bronchopleural fistulae after chest tube placement (Pediatr. Radiol. 1999;29: 87-91).

Three of these children had a surgical chest tube placed for an average of 7 weeks to treat persistent pneumothorax.

The longer drainage continues, the greater the risk of puncturing a lung. A bronchopleural fistula is a serious complication that can substantially lengthen a hospital stay and recovery time, he added.

"Despite the serious morbidity, massive parenchymal damage, and prolonged hospitalizations, long-term outcome following necrotizing pneumonia is excellent," Dr. Colin and his coauthors wrote. In fact, all patients in the study had a complete clinical resolution within 2 months, he added.

"The good news is you do not have to resect damaged lungs—these young patients have a remarkable ability to recover." ■

Catheter Drainage Lowered Reintervention Rates

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. — Image-guided catheter placement significantly reduced the need for reintervention among children with parapneumonic effusion, compared with needle aspiration alone, according to Dr. Andrew Colin.

"What we are looking for are predictors, something that can help us. We want markers in the pleural fluid that will predict outcomes," said Dr. Colin, director of the division of pediatric pulmonology, Holtz Children's Hospital at the University of Miami/Jackson Memorial Medical Center in Florida.

In a retrospective study, Dr. Colin, lead author Ragheed K. Mitri, and their associates reviewed the medical records, microbial reports, and x-rays of 67 pediatric patients over 5 years (Pediatrics 2002;110: e37). A total of 34 children with effusion had aspiration drainage, while 33 others had percutaneous "pigtail" catheters placed.

Median lengths of hospital stay and complication rates were similar between groups. The primary outcome was a need for reintervention, which occurred in 18 children (27%).

"We found three significant predictors of reintervention," Dr. Colin said at a pediatric pulmonology meeting sponsored by the American College of Chest Physicians.

Children in the aspiration-only drainage group experienced significantly higher reintervention rates. Use of image-guided needle aspiration was associated with a more complicated outcome, vs. image-guided percutaneous catheter drainage (odds ratio, 8.0).

"The second predictor we came up with was pH, much as the literature predicted," Dr. Colin said. Reintervention was more likely with a pH of less than 7.0 vs. greater than 7.0 (OR, 14.3). "If you have a low pH, things are not likely to be good. A pH of 7 is actually quite low compared to the general population."

Glucose was not an independent predictor of bad outcome but had predictive value in conjunction with lower pH, Dr. Colin said. "If your pH is over 7.2, glucose does not matter as much, because you are unlikely to do an intervention anyway."

However, with pH below 7.0 and glucose below 20 mg/dL, a reintervention is required about 75% of the time. "And you should probably do it earlier rather than later," Dr. Colin noted.

Timing is critical, because the effusion can change over time. Intervention is easier during the initial, free-flow phase of parapneumonic exudate. After a period of 48-72 hours, the effusion often becomes more viscous. This is called the fibropurulent phase, during which fibrin accumulates and abundant loculation occurs, Dr. Colin explained.

"So, you have a limited time to intervene—a matter of hours in some cases." The gel-like substance can continue to progress to a third, organizing phase, with increased fibroblast activity.

Loculation of fluid was the third predictor in the study.

"With loculation on the ultrasound, there is an odds ratio of 3.6 that you will have to go back to that chest," said Dr. Colin, who is also professor of pediatrics at the University of Miami.

Therefore, primary catheter placement for parapneumonic effusions should be considered in children who undergo diagnostic thoracentesis, Dr. Colin said. Because of the associations they found, an on-site pH meter and a glucometer could facilitate the tube placement decision. ■

Aggressive Surgery Improved Outcomes in MDR-TB

BY BRUCE JANCIN
Elsevier Global Medical News

KEYSTONE, COLO. — Aggressive resectional surgery has led to markedly improved microbiologic and clinical success in treating multidrug-resistant pulmonary tuberculosis, according to experience with patients at the National Jewish Medical and Research Center in Denver.

The use of surgery to treat MDR-TB patients at the center is associated with a greater than fourfold increased likelihood of an initial favorable response to treatment. Fluoroquinolone therapy also is predictive of an initial favorable response, but only in patients older than 40 years.

"Surgery has become a very significant part of our practice at National Jewish," said Dr. Charles L. Daley, head of the division of mycobacterial and respiratory infections at the center. "We think that in select patients, surgical resection is really important to consider."

The goal of the surgery is to remove cavitary lesions and sections of destroyed lung with a high bacillary burden. The operation is most likely to be successful in patients with focal disease and adequate pulmonary function, said Dr. Daley at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center.

Good surgical candidates are patients with MDR-TB who remain culture-positive after 4-6 months of drug therapy, as well as patients with extensively drug-resistant TB (XDR-TB). The World Health Organization's revised definition of XDR-TB issued in late 2006 describes it as MDR—that is, resistance to at least isoniazid and rifampin—plus resistance to any fluoroquinolone and one of the second-line injectable drugs, namely amikacin, capreomycin, or kanamycin.

The success of the surgical strategy was shown by a retrospective study published in 2004. The study reviewed outcomes in 205 patients with MDR-TB treated at National Jewish during 1984-1998, and compared the outcomes with those of 171 other MDR patients treated there during 1973-1983. All the MDR patients in the review were severely resistant to a median of six TB drugs and treated with a median of six agents while at National Jewish.

Treatment outcomes were better in the more recent cohort. Analysis identified two major reasons why: resectional surgery and fluoroquinolone therapy. These were the two novel elements of MDR-TB management introduced at the center after 1983. Each was an independent predictor of good outcome in the study, said Dr. Daley, who also is a professor of medicine at the University of Colorado, Denver.

The initial favorable response rate, defined as at least three consecutive negative sputum cultures over at least 3 months, was 65% in the 1973-1983 cohort, compared with 85% in those treated during 1984-1998. The overall cure rate improved from 56% in 1973-1983 to 75% afterward. Moreover, the TB death rate fell from 22% to 12%.

In a multivariate analysis, surgery was associated with a 4.6-fold increased likelihood of an initial favorable response to

FYI

Genetic Testing Brochure

The National Cancer Institute is offering an eight-page brochure, "Genetic Testing: What It Means for Your Health and for Your Family's Health." It explains what genetic tests are, lists the different types, tells how they are done, and gives examples of diseases linked to genetic changes that can be detected by these tests. The brochure also provides questions for patients to ask their doctor about the tests. To order free copies, visit https://cissecure.nci.nih.gov/ncipubs/details.asp?pid=4155.

Cystic Fibrosis Web Site for the Public

A new online resource for the cystic fibrosis (CF) community has been launched by Novartis. CFvoice.com features educational activities for CF patients and their families and friends. For young children, an animated character named Zude leads coloring and puzzle activities. For preteens and teenagers, the Wacky Workshop appeals to an interest in science and self-discovery, while streaming-video testimonials feature peers talking about managing life with CF. There are also interactive elements and iTunes access. For young adults, the site discusses issues like transitioning to adult care, independent living at college, careers, and marriage. For caregivers, there are support and information on issues, such as dealing with a newly diagnosed child. To log on, go to www.cfvoice.com.

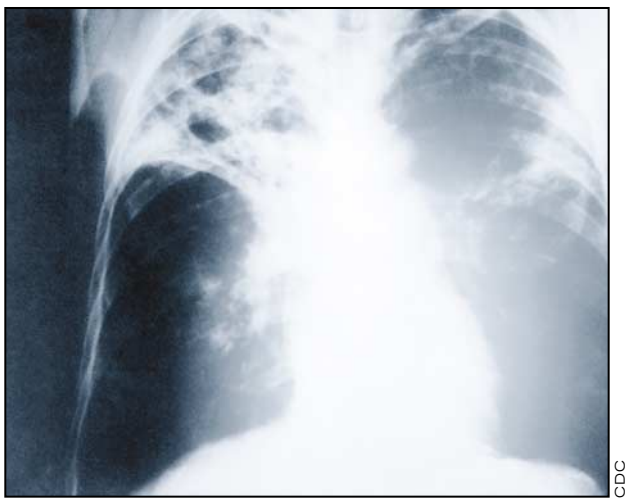
treatment. Fluoroquinolone therapy, introduced in the 1980s, was also predictive of an initial favorable response but only in patients more than 40 years old.

There was a trend toward improved survival in patients who underwent resection. It didn't reach significance, perhaps because of the relatively small sample size (Am. J. Respir. Crit. Care Med. 2004;169:1103-9).

The use of surgical resection climbed steadily at National Jewish over the study years as physicians came to recognize that it resulted in improved outcomes and had a low complication rate. Just 4% of patients treated for MDR from 1973-1983 underwent one or more resectional procedures, compared with 44% discharged in 1984-1988, 63% in 1989-1993, and 83% in 1994-1998.

"This surgery should be performed by experienced surgeons," Dr. Daley stressed. "We used to use a thoracotomy but are now turning to VATS [video-assisted thoracoscopic surgical] resection whenever possible," he said.

Based upon numerous published studies, the predictors of therapeutic failure in patients with MDR-TB include a low body mass index, comorbid HIV, previous therapy, and poor adherence, according to Dr. Daley. ■



CDC

X-ray reveals bilateral infiltrate and "caving formation" in the right apical region in a patient diagnosed with far-advanced TB.

Blood Stored Over 2 Weeks Linked to Adverse Events

BY SUSAN BIRK
Elsevier Global Medical News

Transfusions of red blood cells stored for 15 days or more increase the risk of serious complications and both short- and long-term mortality following cardiac surgery, according to a retrospective study of more than 6,000 patients.

"The relative risk of postoperative death is increased by 30% in patients given blood that has been stored for more than 2 weeks," wrote Dr. Colleen Gorman Koch and her colleagues at the Cleveland Clinic Foundation.

Earlier studies comparing older and newer blood have yielded conflicting results. These studies examined small or heterogeneous samples, did not control for confounding factors, and used end points that did not reflect specific organ function, such as length of hospital stay.

The present study analyzed data on 3,130 cardiac surgery patients transfused with 10,782 units of blood stored for more than 14 days and 2,872 patients transfused with 8,802 units of blood stored for 14 or fewer days during cardiac surgery at Cleveland Clinic between 1998 and 2006. It excluded patients whose transfusions consisted of both newer and older blood and those with trauma and heterogeneous chronic diseases.

Patients underwent coronary artery bypass graft surgery, cardiac valve surgery, or a combination of the two.

The older and newer blood groups shared similarities on most baseline and operative variables. The primary end point was a composite of in-hospital adverse events defined by the Society of Thoracic Surgeons. Follow-up survival status was obtained from the Social Security Death Index (N. Engl. J. Med. 2008;358:1229-39).

The study found a significant association between blood storage time and the serious adverse events composite end point, which occurred in 22.4% of the patients who received newer blood and 25.9% of those who received older blood. The link remained after adjusting for coexisting conditions and other risk factors. Patients transfused with older blood, compared with those who received newer blood, had significantly higher rates of in-hospital mortality (2.8% vs. 1.7%), prolonged ventilation (9.7% vs. 5.6%), renal failure (2.7% vs. 1.6%), septicemia or sepsis (4.0% vs. 2.8%), and multisystem organ failure (0.7% vs. 0.2%).

Risk of death was significantly lower among patients who received newer units of blood; 1-year death rates were 7.4% and 11.0% for the newer and older blood groups, respectively.

TRANSFUSIONS WITH OLDER BLOOD LED TO HIGHER RATES OF PROLONGED VENTILATION, RENAL FAILURE, SEPTICEMIA, AND MULTISYSTEM ORGAN FAILURE.

The mortality increase among older blood patients was most pronounced within 6 months of surgery.

"The adverse effects of transfusing older blood persisted even after adjustment for perioperative factors known to be associated with an adverse outcome in this population," the researchers wrote (data were not presented). These findings warrant further study before any broad-based changes in blood banking practices are made, they said.

The results of the investigation, while important, are not enough to change blood supply practices, said Dr. John W. Adamson in an accompanying editorial. Because the study population had a median age of 70 years, "by definition, the patients had a substantial number of coexisting illnesses."

He also noted that the result could reflect a problem unique to cardiopulmonary bypass, because all the patients underwent that procedure.

Blood management and blood conservation programs, to reduce the amount of transfused blood used in surgeries, would be the most effective course of action, said Dr. Adamson of the Veterans Affairs San Diego Health System, University of California, San Diego. ■

Dr. Philip Marcus, FCCP, comments:
These findings support previous findings and give weight to a widely held belief about transfused blood, i.e., the newer the better. Old blood can be thought of as "bad blood." Although this study involved only older patients undergoing coronary and heart valve surgery, the findings may be applicable to other populations, as well.

CMS Adds Patient Satisfaction to Hospital Web Site

BY JOYCE FRIEDEN
Elsevier Global Medical News

ARLINGTON, VA. — Now that the Centers for Medicare and Medicaid Services has added patient satisfaction data to its Hospital Compare Web site, patients will have more to consider when they decide which hospital to use for an elective procedure.

The Web site already included hospital-specific information on clinical measures, such as antibiotic prophylaxis before surgery and aspirin upon admission for a heart attack. New patient satisfaction data include items such as nurse communication and hospital room cleanliness.

"This is like Travelocity for health care," said Health and Human Services Secretary Mike Leavitt. "When people have information and they have choice, they make good choices." Mr. Leavitt spoke at the annual meeting of the Association of Health Care Journalists.

The patient satisfaction data come from the Consumer Assessment of Healthcare Providers and Systems, a survey administered by 2,500 hospitals to patients discharged between October 2006 and June 2007. The survey included 27 questions about patients' hospital experience, including communication with doctors and nurses, responsiveness of hospital staff, cleanliness and quietness of the hospital environment, and pain management.

The database also will include the volume of certain elective procedures provided at the hospital as well as what Medicare pays for those procedures.

The Centers for Medicare and Medicaid Services (CMS) Deputy Administrator Herb Kuhn said the information will be valuable even if patients already have selected a hospital for an elective procedure. "There are three reasons people pick a hospital," he said in an interview after Mr. Leavitt spoke. "They heard it was good, it's where their physician spends a lot of his time, or it's convenient to them. We want to add another dimension here for people to understand: Okay, if that's where you're going, what do you know about this place?"

The database also will be a good motivator for hospital improvement, Mr. Leavitt said. "Wherever in health care there's robust information about quality and cost, the cost goes down and the quality goes up," he said.

Mr. Leavitt stressed that CMS was not posting the data in order to punish hospitals that aren't performing as well as others. "This is not about eliminating anyone; it's about improving everyone," he said. "The minute a provider sees that they are at lower quality than the marketplace requires, they improve."

As for whether those hospitals that don't improve might eventually face consequences, "I hope so," Mr. Leavitt said. "This is about transparency and accountability. Without consumers and regulators and others having a means of measurement, we continue to reward mediocre—and in some cases, poor—performance.

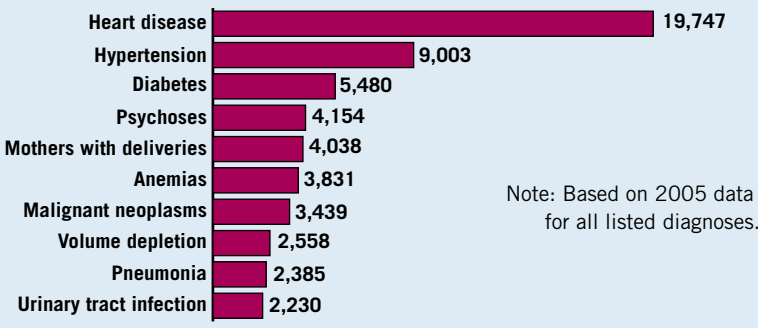
"While this is not about eliminating [hospitals that] are not performing well, we should certainly not assume that the poor performers will not be eliminated, either by the marketplace or by those who oversee quality," Mr. Leavitt explained.

But it's not only hospitals and patients who can use the new data, according to Gerald Shea, assistant to the president for governmental affairs at the AFL-CIO.

"This is important for physicians and other clinicians," he said at the meeting. "We hope physicians take this information and make it part of their regular, routine discussions with their patients." ■

DATA WATCH

Top 10 Diagnoses for Discharges From Short-Stay Hospitals
(in thousands)



Source: Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS

Adenotonsillectomy May Not Resolve Sleep Apnea

Lower-than-expected success rate in a study of 110 children has come as a 'jolt.'

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. — Although adenotonsillectomy remains the first-line treatment for children with obstructive sleep apnea syndrome, only about 25%-30% will experience complete resolution of symptoms, according to a prospective study.

Another 25% or so of children will still have apnea severe enough to warrant continuous positive airway pressure (CPAP) therapy. Management of the children who end up better but not cured after tonsillectomy and adenoidectomy (T&A) remains unclear. About 45% of children "will be neither here nor there. Not cured, but not worse—somewhere in the middle," said Dr. David Gozal, FCCP, director of the division of pediatric sleep medicine, Kosair Children's Hospital Research Institute, University of Louisville (Ky.).

That figure comes from a prospective study of 110 consecutive children with obstructive sleep apnea assessed with polysomnography before and after T&A (J. Pediatr. 2006;149:803-8). Mean age was almost 7 years, and 62% of patients were boys. A total of 37% were obese, the mean body mass index was 24 kg/m^2, and average time between sleep studies was 6.4 months. Outcome was measured as change in the obstructive apnea/hypopnea index (OAHI), defined as the number of instances of apnea and hypopnea per hour of total sleep time.

The overall OAHI before T&A was 24, and at a second polysomnography, it was 5.3, Dr. Gozal, lead author Dr. Riva Tauman, and their associates found. Although a statistically significant improvement, "it was not normal at all—don't expect it to normalize," Dr. Gozal said at a pediatric pulmonology meeting sponsored by the American College of Chest Physicians.

"You don't know who is going to respond or not. It is very difficult to predict results in individual patients," Dr. Gozal said. "But, globally, the percentage who had a normal respiratory pattern after T&A was less than 30%. That is a jolt [and] not the 80%-85% success rate from ENTs that we quote for parents."

In the study, 28% of children scored an OAHI of 1 or less after surgery. Another 27% scored a postoperative OAHI of 5 or greater and were recommended for CPAP.

Because treatment options for the group with residual, mild sleep-disordered breathing after T&A are unclear, Dr. Gozal and colleagues launched another investigation (Pediatrics 2006;117:e61-6). They identified 22 children who had incomplete resolution of sleep apnea postoperatively on polysomnography at 10-14 weeks (an OAHI greater than 1 and less than 5) and treated them for 12 weeks with anti-inflammatory combination therapy. An additional 14 children not treated served as controls.

Patients received oral montelukast, because leukotriene modifiers have been demonstrated as effective for mild sleep-disordered breathing (Am. J. Respir. Crit. Care Med. 2005;172:364-70). They also received intranasal budesonide. Upper airway collapsibility and presence of mild sleep-disordered breathing after T&A might indicate residual upper airway inflammation that could respond to anti-inflammatory treatment, Dr. Gozal said.

Parameters measured during the polysomnography prior to anti-inflammatory therapy were not statistically different between treated and control children. The mean OAHI was 3.9 per hour of total sleep time (TST) in the treatment group and 3.6 per hour of TST in control patients. Researchers also noted similar nadir arterial oxygen saturations (87.3%) and respiratory arousal index findings (4.6 per hour of TST) for both groups. "Sleep fragmentation seems common in these children," Dr. Gozal said.

The posttreatment polysomnography, however, indicated some significant improvements in the treated group, compared with controls. In fact, 21 out of the 24 patients in the treated group normalized their sleep apnea, Dr. Gozal said. The treatment group showed significant improvements in OAHI (0.3 per hour of TST), in nadir arterial oxygen saturation (92.5%), and in respiratory arousal index (0.8 per hour of TST). No significant changes were seen over time in the control group children.

"Although randomized, double-blind, placebo-controlled trials are needed to confirm the current findings, the present study clearly establishes the beneficial role of anti-inflammatory approaches for asymptomatic children with mild sleep-disordered breathing after T&A," Dr. Gozal said.

Dr. Gozal disclosed he is on the national speakers bureau for Merck & Co., which manufactures montelukast. ■

INDEX OF ADVERTISERS

Too Much, Too Little Sleep Doubles Death Risk

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS — Change in sleep duration during midlife is associated in a U-shaped fashion with risk for death more than a decade later, Dr. Francesco Cappuccio reported at a conference of the American Heart Association.

The major driver of increased mortality among individuals at the low end of the sleep duration continuum is an excess of cardiovascular deaths, while in long sleepers, the increase in mortality is due to noncardiovascular causes, according to the results of the Whitehall II study, said Dr. Cappuccio of Warwick Medical School, Coventry, England.

Whitehall II is a prospective cohort study of 10,308 white-collar British civil servants who were 35-55 years old when enrolled in the study in 1985-1988. Because work, parenthood, and other demands on time make sleep deprivation pervasive in contemporary society, Dr. Cappuccio and his coworkers decided to study whether lack of sleep carries a price in terms of mortality.

The Whitehall II analysis of the impact of changes in sleep duration included information on baseline sleep patterns in 7,729 participants and changes in those patterns over the next 5 years. Participants then were followed for mortality through 2004.

Cardiovascular mortality was 2.4-fold higher among subjects who slept an average of 6-8 hr/night at baseline but cut their sleep duration to 5 hr/night or less over the next 5 years' follow-up, compared with those who held fast to the 6- to 8-hour pattern. The findings held after adjustment for potential confounding factors including age, gender, employment grade, marital status, blood pressure, body mass index, alcohol intake, smoking status, comorbid illnesses, and physical activity.

In those who increased their sleep duration from 7-8 hr/night at baseline to 9 or more, there was an adjusted 2.1-fold increase in noncardiovascular mortality.

Short sleep duration is known to be associated with hypertension, weight gain, and diabetes, all of which increase cardiovascular risk. In contrast, the mechanism for the relationship between long sleep and increased mortality is unclear. Hypotheses include possible links with depression and cancer-related fatigue, added Dr. Cappuccio. ■

Sleep-Disordered Breathing More Common in Obese Inpatients

BY LEANNE SULLIVAN
Elsevier Global Medical News

Sleep-disordered breathing in hospitalized patients is more common in those who are obese and those who have heart failure.

"There may be more [sleep-disordered breathing] in hospitalized patients than has been recognized," concluded Dr. Kim Goring and Dr. Nancy Collop, FCCP, of Johns Hopkins University Hospital and Bayview Medical Center, both in Baltimore.

"There is a need for a higher clinical suspicion, especially in patients with underlying cardiopulmonary disease," they said.

In a chart review of 94 inpatients referred for polysomnography at two tertiary care facilities, a body mass index (BMI) of 40 kg/m^2 or greater was associated with a statistically significant increase in the risk of sleep apnea (odds ratio, 9.81), compared with a normal BMI of 18-24, they reported.

The patients (51 women, 43 men) were admitted to Johns Hopkins or Bayview between January 2003 and September 2004 for acute illnesses, mostly chronic obstructive pulmonary disease or heart failure; the next most common diagnoses were interstitial lung disease, acute pulmonary embolism, and pulmonary hypertension. Mean age was 54 years (range, 20-82 years), and mean BMI was 40 (range, 18-70). Of the total sample, 86% were obese (BMI greater than 30), the researchers said.

The patients underwent overnight polysomnography to detect sleep apnea (defined as complete or almost complete cessation of airflow—less than 25% of baseline—lasting 10 seconds or longer), and hypopnea (defined as a fall in oxygen saturation of at least 4%, or an arousal from sleep). An apnea-hypopnea index (AHI) greater than 10 was classified as sleep-disordered breathing (J. Clin. Sleep Med. 2008;4:105-10).

Of the 94 patients, 77% had sleep-disordered breathing, and of those with the condition, 95% had obstructive sleep apnea.

"This high prevalence of [sleep-disordered breathing] is most likely due to the overwhelming influence of obesity," Dr. Goring and Dr. Collop wrote. They found "a statistically significant increase in the [operating room] of sleep apnea with every unit increase in BMI adjusting for all other variables," with the vast majority of the study patients with a BMI over 40 positive for sleep apnea. Weight has been shown to strongly predict sleep-disordered breathing. In this study, "there was a probable bias on the part of the referring physicians in targeting obese patients for inpatient polysomnography, given that 86% of those referred were obese."

Although 60% of normal-weight patients with interstitial lung disease, neuromuscular disease, or acute pulmonary embolism had sleep-disordered breathing, it was difficult to draw statistically significant conclusions because of the small numbers of subjects, they wrote.

The association between sleep apnea and heart failure was significant, but the investigators cited difficulty in assessing the effect of obesity on the likelihood of sleep-disordered breathing in patients with heart failure. No link was found between sleep apnea and any of the other acute illnesses in these patients.

The study was supported by grants from the National Institutes of Health. Neither researcher had a financial conflict of interest. ■

Pulmonary Perspectives

Management of Respiratory Acidosis in Low Tidal Volume Ventilation: Part 1

Mechanical ventilation for patients with respiratory failure can induce or exacerbate lung injury, presumably through high shear forces generated from overdistention and cyclic opening and closing of lung units.

Research in animal models and clinical studies of patients with asthma and acute lung injury (ALI) undergoing mechanical ventilation have demonstrated that a strategy of low tidal ventilation with positive end-expiratory pressure (PEEP) can attenuate the lung injury induced by the ventilator and improve clinical outcomes (*N Engl J Med* 2000; 342:1301). In addition, there are some data suggesting that a reduction in tidal volume in all patients with respiratory failure may reduce the risk of ventilator-associated lung injury (Gajic et al. *Crit Care Med* 2004; 32:1817).

A necessary consequence of this approach is some degree of hypoventilation, which leads to hypercapnia and respiratory acidosis. Given the widespread use of protective ventilatory strategies while tolerating respiratory acidosis (an approach termed "controlled hypoventilation" or "permissive hypercapnia"), understanding the effects and management of respiratory acidosis is essential.

Case series and clinical studies have suggested that hypoventilation and moderate respiratory acidosis can be well tolerated in patients with respiratory failure (*N Engl J Med* 2000; 342:1301; Gajic et al. *Crit Care Med* 2004; 32:1817), although the exact cutoff of an acceptable arterial pH or CO_2 has not been determined.

Unfortunately, there is very little to guide us in terms of randomized controlled trials; thus, defining a "safe" pH and CO_2 will depend, in part, on characteristics of the patient's illness (*ie*, hemodynamic stability, arrhythmias, cerebral edema, etc), as well as the clinical judgment of the care team.

In a landmark study (Hickling et al. *Crit Care Med* 1994; 22:1568), the authors demonstrated a relatively low mortality rate (26%) in patients with ARDS ventilated with low tidal volumes. These patients had a mean arterial CO_2 of 67 mm Hg and a mean pH of 7.23 without apparent adverse outcomes. However, it should be noted that hypercapnia and respiratory acidosis can lead to arrhythmias, cardiac depression, pulmonary hypertension, prolonged weakness, and increased cerebral blood flow, and may raise intracranial pressure. Fortunately, these changes are largely attenuated when there is a gradual development of acidosis (Hassett and Laffey. *Crit Care Med* 2007; 35:2229).

In addition, patients managed with controlled hypoventilation often require fairly high doses of potent sedatives in order to tolerate the discomfort of a respiratory acidosis, and, thus, may have an increased risk of complications related to increased sedation.

THE DATA DO SUGGEST THAT WHEN CAREFULLY APPLIED, CONTROLLED HYPOVENTILATION WITH RESPIRATORY ACIDOSIS CAN BE WELL TOLERATED.

These data suggest that although it appears that hypercapnic acidosis can be well tolerated, in theory, there could be some point where the benefits of controlled hypoventilation are outweighed by adverse effects of respiratory acidosis.

Despite the potential complications of hypercarbic acidosis, research in animal models has suggested that respiratory acidosis and hypercapnia may actually have beneficial effects in the setting of ventilator-induced lung injury, sepsis, ischemia-reperfusion injury, and shock (Hassett and Laffey. *Crit Care Med* 2007; 35:2229).

In addition, on the cellular level, respiratory acidosis may attenuate cytokine release, free radical production, capillary permeability, and lactic acidosis (Ni Chonghaile et al. *Curr Opin Crit Care* 2005; 11:56).

These beneficial effects are thought to be related to the acidosis, although there may be some additional benefit from hypercapnia. However, more recent research has suggested that hypercapnia can lead to alveolar epithelial cell dysfunction and, thus, may also have detrimental effects in respiratory failure (Vadasz et al. *J Clin Invest* 2008; 118:752).

Recent secondary analysis of patients in the ARDS network study has demonstrated reduced mortality in patients with hypercapnic acidosis, only in the group ventilated with large (12 mL/kg) tidal volumes (Kregenow et al. *Crit Care Med* 2006; 34:1).

Although these data suggest a potential clinically relevant benefit for respiratory acidosis, there are no definitive data comparing the effects of hypercapnic respiratory acidosis on outcomes independent of the levels of lung stress. Thus, it is unclear whether respiratory acidosis is truly beneficial in the management of patients with respiratory failure, independent of the ventilatory strategy used.

The data do suggest, however, that when carefully applied, controlled hypoventilation with respiratory acidosis can be well tolerated and used without serious adverse events. ■

Dr. Benjamin D. Medoff
Assistant Professor of Medicine
Center for Immunology and Inflammatory Diseases
Pulmonary and Critical Care Unit
Massachusetts General Hospital
Boston, MA

Watch for Part 2 on this topic in the June issue of *CHEST PHYSICIAN*.

Editor's Note

Dr. Medoff raises intriguing and clinically relevant questions for practicing intensivists. We now understand that controlling tidal volume and plateau pressures in patients with the acute respiratory distress syndrome has an important impact on survival. Unfortunately, there are concerns with this strategy, particularly when hypercapnic respiratory acidosis is a complicating factor. It might be worthwhile for all of us who care for these patients to reconsider our approach to managing respiratory acidosis when low tidal volume ventilation leads to hypercapnia.

Dr. Gene L. Colice, FCCP
Editor,
Pulmonary Perspectives

NEWS FROM THE COLLEGE

PRESIDENT'S REPORT

Capitol Hill Caucus: Reaffirming the Need for Our Involvement

I attended the ACCP 15th Annual Capitol Hill Caucus in early April. It was a wonderful event. There were more than 75 attendees (in past years, 40 to 50 attendees was considered a good year). Twenty-eight attendees were ACCP Governors (37%) and 26 were at-large attendees (35%). Some of our sister organizations were also represented by our members and attendees, including the ATS, NAMDRC, AACN (American Association of Critical-Care Nurses), and the Alpha-1 Foundation.

BY DR. ALVIN V. THOMAS, JR., FCCP

The discussions the first day, as well as during our Capitol Hill visits to our congressmen, were focused on four primary issues:

- Pulmonary rehabilitation legislation
- The critical care workforce crisis
- Medicare physician payment reform
- The Family Asthma Act

Day 1—Morning: Attendees were updated on the primary issues of each bill. As part of that discussion, one of the attendees was asked to give a personal patient-related vignette that was illustrative of the need and practical impact of each bill. This was done so that each attendee could get a feel for how important such vignettes are when addressing the congressmen. The need and importance for each piece of legislation is so much more urgent when we relate it to personal experiences and impact on our patients.

I was asked to give a patient example of the need for the Family Asthma Act. It is a bill initiated by Senator Hillary Clinton (with direct consultative input by ACCP member Dr. Irwin Berlin, FCCP) that would provide federal support for innovative interventions (grants), particularly in underserved patient communities, that would help prevent and control asthma and improve patient self-management of the disease.

The example I gave was an adult asthma patient who lives in the southeast area of DC, an area where asthma per capita health statistics are among the worst in the country. She had an acute asthma attack but did not feel confident about going to local acute care facilities (especially after the closure of DC General Hospital several years ago and the financial and health delivery challenges of the local acute care facilities). She, therefore, did not call 911 for an ambulance but, instead, took two city buses to our facility (Howard). There, she walked into the ED, collapsed, was intubated, mechanical ventilation was initiated, and she was admitted to our medical ICU. She survived to tell the story!

Such a story is indicative of the great disparities in care throughout our country and the particular disparities in asthma care. It is the kind of story that resonates with our congressmen. A bill such as the Family Asthma Act is essential if we are to begin to close the disparity gap.

Day 1—Afternoon: Several of our attendees engaged in role playing with former Representative Jim Davis (now employed by our legislative counsel in DC, Holland & Knight). It was quite effective. Selected attendees were asked to model a congressional visit on each of the four bills with Mr. Davis, who was tough and effective in his role of a congressman! The presentations were critiqued by the audience and Mr. Davis. It was an excellent example and teaching tool for our congressional visits the next day.

Day 2—Morning and afternoon: A briefing was held by several congressmen and senators (bipartisan representation of Republicans and Democrats) on the status of the four bills in Congress. The speakers included four physicians. The presentations were quite interesting and helpful. Next, we visited Capitol Hill (Senate and House of Representatives offices), where we each interacted with our local congressmen and senators (in most cases their legislative aides). We were expected to lobby on each of the four bills and reiterate our support for FDA regulation of tobacco.

Day 2—Evening: We met back at the hotel to relate our experiences of the afternoon, the results of which were generally diverse. Some congressmen were quite supportive of almost all bills and FDA tobacco regulation. Others were not as supportive of the tobacco issue or knowledgeable about the critical care workforce issue or pulmonary rehabilitation. Most were supportive of Medicare physician payment reform, and they accepted the fact that the SGR (sustainable growth rate) is flawed but were inclined to continue delay of a true solution to the SGR problem. Virtually all congressmen were unaware of the Family Asthma Act. Much work needs to be done on this issue if the bill is to be considered and passed.

In summary, the caucus this year was well-organized, stimulating, and informative. It served as a reaffirmation for me of the need for all of us, as physicians, to take our heads out of the sand and get more involved in providing information and feedback to our government representatives, especially at the local, grassroots level. The stakes are too high, especially in a year when health-related issues are so central to our national political discourse. Get involved! Contact your local ACCP Governor for help or the ACCP Government Relations Committee staff (Lynne Marcus at lmarcus@chestnet.org). Your input and involvement are essential. ■

Product of the Month: Web Updates on ICU Hypertensive Crises, Pneumonias

View the newest ACCP educational products available online, which feature information from CHEST 2007 satellite symposia. The information also was published as supplements accompanying the April issue of CHEST PHYSICIAN.

▶ **Hypertensive Crises in the Critical Care Setting: Current Perspectives and Practice Challenges**—A review of hypertensive emergencies, which includes a spectrum of clinical syndromes and a focus on specific drugs and therapeutic strategies available in the ICU.

▶ **Clinical Challenges and Case Studies of Microorganisms in Pneumonias**—Addresses the challenging issues surrounding the recognition and management of pneumonia. Infectious disease specialists offer their insight into current issues and standards related to bacterial pneumonia. Clinicians involved in the care of patients with pneumonia will find the information timely and readily applicable to clinical practice.

To view and download, visit the ACCP online education site at www.chestnet.org/education/online/index.php. ■

NEWS FROM THE COLLEGE

ACCP Sleep Institute 2008 Echo Poll: Physician Sleep Habits and Productivity

BY ROCHELLE GOLDBERG, MD, FCCP
Member, ACCP Sleep Institute Steering Committee

Background

This year's Sleep in America Poll evaluates sleep habits and productivity in the workplace. Results from this large and increasingly high-profile poll were made available to the public during National Sleep Awareness Week, which is traditionally the first week of March. Continuing our tradition of partnering with the National Sleep Foundation (NSF) on important aspects of sleep health, the ACCP Sleep Institute Steering Committee worked with NSF to develop an echo poll (a separate poll that asks similar questions as the "parent" poll but to a different and usually smaller audience) that assessed the sleep habits and work productivity of ACCP members.

Methods

A task force of the ACCP Sleep Institute Steering Committee developed the questions used for the echo poll. The poll consisted of 30 multiple response questions and one open-ended comment section.

The poll, which was administered through the ACCP Web site via an online survey tool, was sent to 5,006 randomly selected US ACCP physician members. In order to maximize the response rate, requests for responses were sent out at weekly intervals, three times, from December 17, 2007, to January 3, 2008.

The goal of our poll was to "echo" the NSF's Sleep in America Poll, in that, when possible, the responses of the physician population were compared with those obtained by the Sleep in America Poll.

FCCP Responses

There were 581 responses (12.1%) by the time the poll ended on January 7, 2008. Of the respondents, 73.6% were white, 2.3% were African-American, 6.3% were Hispanic, and 13.9 % were Asian. Married or partnered respondents made up the majority of the population (89.9%). Most respondents (84.3%) were ACCP members for at least 6 years (range 6 to >20 years), and 87.8% were in medical practice for more than 6 years (range 6 to >20 years). General health was perceived as good, very good, or excellent in 97.9% of respondents. Physician respondents were largely satisfied with their work (79.7% were satisfied or very satisfied) and had mostly positive interactions with others at their workplace (96.8% reported good, very good, or excellent interactions).

Regarding work routines, which were the focus of the poll, most practitioners start their workday between 7:00 AM and 9:00 AM and finish between 5:00 PM and 8:00 PM. Bedtimes and wake-up times did not vary much across workdays and non-workdays. The majority of respondents indicated that their bedtime was between 10:00 PM and midnight. The majority of respondents also indicated that their wake-up time was between 5:00 AM to 7:00 AM on workdays and between 6:00 AM and 9:00 AM on days off.

Sleep amounts varied from 6.5 h on work nights and 7.5 h on days off. In contrast to the average physician practice, most physicians claimed that 7 to 8 h of sleep would be optimal. The number of caffeinated beverages consumed by physicians averaged three daily. Most physicians who consumed caffeine saw this as a "habit" (83.3%), rather than a strategy to "keep awake."

Difficulty initiating or maintaining sleep was rare in this population, although almost 30% did not feel refreshed upon awakening. Close to half (43.1%) of the respondents did not feel that their work schedule allowed for adequate sleep time. Sleepiness interfering with daily activities was rarely noted, although 10.1% reported this problem a few days a week.

A small minority of physicians noticed measurable sleepiness at work in a usual month, and 27.2% admitted to napping or dozing at work in the preceding month. However, on a more subtle level, frequent (at least a few days a week) challenges with concentration, organization, and task completion were noted in 5 to 10% of people. This did not contribute to work injuries or accidents and rarely resulted in the missing of work or family functions.

Snoring was acknowledged in 26.4% of respondents, and 27 members have been treated for sleep apnea. One percent each reported treatment for restless legs syndrome or insomnia.

Ninety-nine physicians included specific comments with their surveys. While qualitative, several themes emerged. Lifestyle issues (*eg*, small children, social and volunteer commitments) also were identified as determinants of sleep for 13 people. Not surprisingly, night call played a significant role in sleep quality for 38 people relating to their sleep that night, as well as in anticipation of a call night. Eleven physicians described some personal sacrifice or impact on health relating to sleep. Four individuals were contemplating a change of job because of sleep difficulties.

Comparison With the NSF Poll

Results for physicians and the general population were similar in terms of average reported sleep at night, as well as perceived sleep needs. More physicians responded that work prevented adequate sleep time and that they had missed at least one family event due to sleepiness. Caffeine use was more common in physicians than the general population (93% vs 82%), although average consumption in those who consumed caffeine was similar (approximately three servings daily). In general, more physicians reported very good to excellent health than the general population (83.6 vs 56.0%).

Discussion and Implications

Physicians identify a gap in their perceived sleep needs vs what they obtain on a regular basis. A somewhat longer time in bed on days off supports this perception and is similar to the general population. Nonetheless, despite what might be considered mild sleep deprivation, most physicians do not indicate that sleep deprivation leads to a significant impact on work performance or responsiveness to other daily concerns. Habits, such as caffeine intake, are not much different in those who consume caffeine compared with those who do not consume caffeine, although more physicians indicated a caffeine "habit" than the general population.

The echo poll findings have some potential limitations. One consideration is the presence of response bias. Are the FCCPs who chose to respond to this poll the good and happy sleepers or the less satisfied lot? If physicians are challenged by lesser amounts of sleep and workplace fatigue, do they recognize it in themselves? Finally, how do physicians' sleep habits affect their ability to relate to patients who have sleep disorders or problems with sleep?

Despite these limitations, the echo poll provides the ACCP Sleep Institute with a useful snapshot of the "state of sleep" of what is likely a representative group of FCCPs in practices across the country. The take home message is that a significant number of pulmonary physicians (Dare we extrapolate to other physicians?) are modestly sleep-deprived but, nonetheless, seem to get through their days in a satisfactory manner. A minority of subjects seemed to be truly struggling with sleep deprivation.

Evidence from recent research over the past 5 years has started to link even relatively modest degrees of chronic sleep deprivation with adverse health, such as weight gain, insulin resistance, and decreases in vigilance. While these research findings should still be considered preliminary, it may not be too early to consider getting adequate sleep. To borrow a slogan from the NSF, sleep is "as important as good nutrition and exercise, only easier." ■

This Month in *CHEST*— Editor's Picks

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

▶ **Safety of Long-Acting Beta-Agonists in Stable COPD: A Systematic Review.** *By Dr. G. J. Rodrigo, et al*

▶ **Is Metalloproteinase-7 Specific for Idiopathic Pulmonary Fibrosis?** *By Dr. J. W. Huh, et al*

▶ **A Web-Based Delphi Study on the Indications of Chest Radiographs for Patients in ICUs.** *By Dr. G. Hejblum, et al*

▶ **Ventilator Settings and Outcome of Respiratory Failure in Chronic Interstitial Lung Disease.** *By Dr. E. R. Fernández-Pérez, et al*

Point/Counterpoint Editorials

▶ **Evidence-Based Medicine Has a Sound Scientific Base.** *By Dr. P. J. Karanicolas, et al*

▶ **Evidence-Based Medicine Lacks a Sound Scientific Base.** *By Dr. M. J. Tobin*

Supplement

▶ **Definitive Care for the Critically Ill During a Disaster.** *From a Task Force for Mass Critical Care Summit Meeting, Jan 26-27, 2007*

www.chestjournal.org

NEWS FROM THE COLLEGE

NETWORKS

Reaching Affiliates, Removing Tobacco Promotions

Affiliate

By Dr. Kevin Chan, FCCP, NetWork Chair

The American College of Chest Physicians strives to offer health-care providers in the specialties of pulmonary, critical care, cardiology, thoracic surgery, and sleep medicine an avenue for educational and practice resources, opportunities for presentation and discussion of scientific information, and opportunities for leadership. The Affiliate NetWork concentrates these goals toward the fellow-in-training and physicians early in career development. There are currently 2,400 affiliate members of the College who have access to discounts on many educational activities. In addition, the ACCP offers opportunities for publication and presentation specifically for affiliate members.

Activities of particular interest to affiliate members include the annual pulmonary, critical care, and sleep medicine review courses, ABIM-sanctioned SEP Pulmonary and Critical Care Module reviews, and the ACCP-SEEK pulmonary, critical care, and sleep mini-board preparation courses offered at CHEST. In addition, many affiliate members are benefiting from the hands-on learning experiences provided by the ACCP's new simulation center. Affiliate members made up 40% of participants at the clinical simulation sessions at CHEST 2007.

The Affiliate NetWork offers members the opportunity to present case reports and scientific abstracts at the annual CHEST meetings. The CHEST Challenge is also spearheaded by the Allied Health NetWork and continues to involve an increasing number of pulmonary and critical care medicine training programs. Each year at the CHEST meeting, fellows-in-training from various programs compete as teams in live, game-show-style rounds.

Responding to membership needs in the area of career development after fellowship, questions on contract negotiations, practice lifestyle, types of practices, and how to find the right job were the focus of new presentations at CHEST 2007. The Affiliate Luncheon presentation by Dr. Michael Nelson, FCCP, Chair of the Private Practice NetWork, *Transition From Fellowship to Practice: Picking a Private Practice,* was well received. Plans are underway to partner with the Private Practice NetWork to develop a course on choosing a career and finding the right practice. Please visit the newly designed Web pages at www.chestnet.org/networks/affiliate to find out how to become involved with the Affiliate NetWork. We look forward to working for you and with you soon.

Airways Disorders

By Dr. Paula Anderson, FCCP, NetWork Chair

Dr. William Calhoun, FCCP, gave the special presentation at the Airways Disorders NetWork Open Meeting at CHEST 2007 on "Noninvasive Measures of Airway Inflammation." These measurements can reflect airway inflammation in asthma and include invasive tests (bronchial biopsy and bronchoalveolar lavage), as well as noninvasive tests (induced sputum, exhaled breath analysis, and methacholine or mannitol challenge). To date, these types of tests are not included in asthma clinical practice guidelines as outcomes measures for asthma control, and Dr. Calhoun discussed their relevance in clinical practice. He summarized that the noninvasive markers lack a "gold standard" of airway inflammation but may be reflective of important asthma outcomes. Several markers have good predictive value for important asthma outcomes, such as the use of induced sputum analysis or exhaled nitric oxide to gauge the need for additional inhaled corticosteroids. Dr. Calhoun also stated that exhaled nitric oxide and mannitol challenge testing are nearing clinical applicability.

The slides used for his presentation can be found on the Airways Disorders NetWork Web page at www.chestnet.org/networks/airway_disorders/index.php.

Another controversial area in asthma therapy involves safety of long-acting beta$_2$-agonists (LABAs). The US Food and Drug Administration issued a black box warning for LABAs in 2005 based on literature suggesting asthma mortality was increased with LABAs. The Airways Disorders NetWork Steering Committee wanted to investigate whether the black box warning has influenced the practice of specialists and primary care physicians and developed a NetWork project to survey practitioners about LABA use. A questionnaire was distributed to members of the ACCP, the American Academy of Allergy, Asthma and Immunology (AAAI), the American Academy of Family Practice (AAFP), and the American College of Physicians (ACP). There were 1,107 physicians who responded. Analysis of the results showed very interesting effects of the black box warning on the different specialties, and a manuscript is now being prepared for publication.

To learn more about the ACCP Airways Disorders NetWork, to get involved, or to suggest a NetWork project, go to www.chestnet.org/networks/airway_disorders/index.php.

Women's Health

How Does the Tobacco Industry Use Your Office To Promote Smoking?

By Virginia Reichert, NP (Steering Committee Member); Patricia Folan, RN; and Susan Kennedy, LMSW

While you are working to make your patients healthy, tobacco companies are advertising in magazines that your patients read in your waiting room. Advertisements in periodicals are the main avenue that the tobacco industry uses to promote their deadly products. Tobacco advertisements normalize tobacco use, undermine tobacco cessation efforts, and encourage youth initiation. In addition, tobacco company advertising can influence and constrain a magazine's ability to report on and accurately convey the health consequences of tobacco use.

Two states have created initiatives to educate health-care providers about these advertisements and to encourage them to allow only tobacco ad-free periodicals in their waiting rooms.

The Maryland State Medical Society, in collaboration with the Campaign for Tobacco Free Kids® and Smoke Free Baltimore County, asked physicians and health-care organizations to sign endorsements that were sent to magazine publishers asking them not to accept tobacco advertising. Learn more about this project at www.medchi.org/grants/tobaccoads/main.asp.

The New York State Tobacco Control Program launched an education campaign that included having physicians request tobacco ad-free copies of magazines. The reasoning was based on an agreement that the National Association of Attorney Generals (NAAG) had reached with Time Inc. and Newsweek Inc., to eliminate tobacco advertising from *People*, *Time*, *Sports Illustrated*, and *Newsweek* magazines that are delivered to schools. Why shouldn't doctors, dentists, and other health-care providers be able to request these same selective bindings to protect their patients?

In addition, health-care providers were educated about the "Quit Assist" displays that had been sent to their offices by Philip Morris. Many physicians were shocked to learn that they were unknowingly displaying these materials in their office.

On the surface, they seem like a good idea, but the cessation message is a soft sell because it is really a public relations campaign. Providers were asked to replace the displays with free state cessation materials that promoted the NYS Smokers' Quitline.

Once made aware, most physicians agree that they would rather not display smoking cessation materials sponsored by tobacco companies and magazines with cigarette ads in their waiting rooms.

For more information on the efforts of the NetWork, visit www.chestnet.org/networks/womens_health/index.php.

Pulmonary Physiology, Function, and Rehabilitation

By Dr. Brian Carlin, FCCP, NetWork Chair

Our NetWork has instituted several changes to its NetWork Web pages at www.chestnet.org/networks/ppfr. These include a section on interesting pulmonary function and cardiopulmonary exercise testing cases, as well as a section on selected up-to-date references in the field.

The NetWork is involved with several important projects. The development of performance measures for pulmonary rehabilitation has been approved and will be designed in a fashion similar to the AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation (Thomas et al. *J Cardiopulm Rehabil Prev* 2007; 27:260). The joint ACCP/AACVPR guidelines published in 2007 (Ries et al. *Chest* 2007; 131[suppl]:4S) will be used as a basis for this document.

Representatives from the major pulmonary organizations are currently being selected to participate in the process.

The NetWork also participated in a response to the recently released, "Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians," (Qaseem et al. *Ann Intern Med* 2007; 147:633). Particular emphasis was placed on the differences between the ACCP/AACVPR evidence-based clinical practice guidelines for pulmonary rehabilitation and the ACP publication.

Ongoing efforts are underway to promote the congressional bills regarding pulmonary rehabilitation and were addressed during the recent ACCP Capitol Hill Caucus. ■

NEWS FROM THE COLLEGE

Educational Resources: The Team Approach

BY SANDRA ZELMAN LEWIS, PHD
Assistant VP, Health and Science Policy and Quality Improvement

Patient care is usually a multidisciplinary effort involving several medical or surgical specialties, nursing, and allied health practitioners. Developing educational resources for the practicing physician and/or support team members also is a multidisciplinary effort.

At the ACCP, this activity is a combined effort involving ACCP members, staff, and consultants working together using a team-based approach.

The Health and Science Policy (HSP), Quality Improvement (QI), and Education departments are under the umbrella of the ACCP Educational Resources Division and work collaboratively in many overlapping areas.

HSP is the department that develops evidence-based clinical practice guidelines, and QI reviews and provides comment on national performance measures and QI projects. Education offers courses and programs, as well as the annual CHEST meeting. All three areas are inextricably linked by the content and applications of their products.

Use of HSP Expertise or Products

The clinical practice guidelines can be the backbone of the various collaborative projects. Educational programs and courses are developed from the guidelines. Several sessions are offered at the annual CHEST meetings that review the latest guidelines. Simulation modules also can be written to teach the guideline recommendations and analyze adherence to the recommendations.

THE PRODUCTS AND OPPORTUNITIES OFFERED WILL BE MORE EVIDENCE-BASED AND MORE APPLICABLE TO THE PRACTICING CHEST PHYSICIAN.

ACCP guideline recommendations will be reviewed for possible development into performance measures by Quality Improvement Committee (QIC) liaisons. Those guidelines that are selected are developed through the Physician Consortium for Performance Improvement, which would require the appointment of several content experts (in this case, guideline authors) to the workgroup.

When the ACCP is requested to comment or vote on pulmonary, critical care, or sleep measures from other organizations, the QIC might request content expertise from guideline panelists, HSP members, or other ACCP members. This is especially important if the ACCP was not involved in the development process and if there are no experts in that particular area on the QIC. The guideline panelists or other content experts would then be requested to assess whether the performance measures conform to the guideline recommendations or evidence.

Use of QI Expertise, Data, or Performance Measures

QIC members will review ACCP clinical practice guidelines after they are completed to determine which of the recommendations, if any, should be developed into performance measures.

The QIC will collaborate with the major national performance measures developers, *eg,* the Physician Consortium for Performance Improvement, to develop the measures and steer them through the endorsement, testing, and implementation processes.

Performance measures can be used in educational programs and courses. Each year, several sessions at the annual CHEST meeting are devoted to quality improvement and performance. As more physicians will be required to report and be measured on their adherence to the performance measures, more education opportunities will be necessary to provide them with the information they need. The QIC can assist with these education programs and sample tools. Simulation modules can assess a physician's compliance with performance measures and gaps in knowledge.

If the ACCP QI database becomes a reality, data will be used to assess compliance with guideline recommendations and knowledge gaps. Educational interventions, including the curriculum developed for the simulation center, could be prepared for physicians with identified knowledge gaps or those opting for additional CME in these areas.

Although there already are many areas of collaboration between the HSP, QI, and Education departments of the College, the volume of collaboration will continue to grow. As a result, the products and opportunities offered to ACCP members will be more evidence-based, more applicable and feasible to the practicing chest physician's practice, and more appropriate for the needs of any particular member.

If you have questions or want more information, contact Sandra Zelman Lewis, PhD, at slewis@chestnet.org. ■

For Whom The CHEST Foundation Serves?

BY ROBERT G. JOHNSON, MD, FCCP
President, The CHEST Foundation

The CHEST Foundation is delighted to be given the opportunity to regularly present itself to the readers of CHEST PHYSICIAN. In these articles, The Foundation leadership shall seek to inform our colleagues about the activities of their Foundation; ever aware that the good works of The Foundation are made possible only by the generosity of the members and partners of the American College of Chest Physicians. In keeping with the well-appreciated style of these pages, our articles shall ever be brief, and, one can only hope, on occasion, fun to read.

Having been involved with The Foundation since its conception, it is sometimes astounding to me how few of my colleagues really know what The Foundation is or does.

It was only a few years ago that an esteemed colleague in a leadership position observed that to many ACCP Fellows, The Foundation is a part of the organization dedicated to a host of fossilized ACCP past presidents. Ouch! As much as it smarted to be categorized as Jurassic, it was impossible for me not to take the observation seriously.

When The Foundation was first envisioned by then-President-Elect Dr. Bart Chernow, Master FCCP, in 1996, the reasons for establishment of an ACCP-supporting foundation were many, and, perhaps naturally, unfocused. "Pluripotent" it was. Among the hopes that laid the foundation's base was the prospect of support for our College's core mission of patient-focused medical education.

Over the years, a long list of talented College members (only a few of whom were ancient, past presidents) defined and refined the focus of The Foundation.

Those foci today are *clinical research, critical care/end-of-life care, tobacco prevention education,* and *humanitarian service.*

Even while defining these core interests, The Foundation has been able to fund over $1 million in humanitarian awards to support 160 projects worldwide, where ACCP members donate their time and invest more than $3 million in clinical research awards to hundreds of members to promote innovations in patient care!

Hundreds of antitobacco educational efforts have been made throughout the country, touching thousands of students' lives and propagating by training an ever-growing group of teachers, while developing enduring tools for their use.

Through our Distinguished Scholar program, we have supported six outstanding investigators whose projects contribute to clinical programs and improvements in critical care, respiratory care, and thrombosis.

Through the sponsorship of the Critical Care Family Assistance Program, now in partnership with the American Association of Critical-Care Nurses, we have improved the experience of hundreds of health professionals and patients in ICUs across the country.

All of this has been accomplished on behalf of the College, in support of its Fellows, its members, and the patients for whom they care.

Even these major accomplishments do not completely represent the contributions of The Foundation. Indeed, soon after its inception, it was charged with managing the ACCP's many honor lectures and awards; endeavoring to better support these financially and to make them consistently relevant to our membership and mission.

In addition, The Foundation has been the home for our *Pro Bono* committee and its many good works in the occasion of disasters at home and abroad. The Foundation serves as the primary liaison with the Palliative and End-of-Life Care NetWork and the Women's Health NetWork. Each of these naturally fit into one or more of our core missions.

These accomplishments should make it clear that although The Foundation was conceived and, initially, nurtured by a small group of dedicated members and staff, it serves the College as a whole, its members, and the world in which we live and work.

In answer to the title's question: *The Foundation serves for thee*, and all who have contributed to these efforts can be proud of the selflessness of your gifts; the extent of your reach.

In future issues of CHEST PHYSICIAN, we will examine how The Foundation has grown since its beginning, through its four foci, ever striving to fulfill its mission of support for the College. ■

NEWS FROM THE COLLEGE

PCCU
PULMONARY AND CRITICAL CARE UPDATE

Provides Educational Opportunities

Take advantage of this unique educational program offered by the ACCP at www.chestnet.org/education/online/pccu/index.php.

Each month, a distinguished editorial board of expert clinicians will provide two lessons, featuring timely, concise, diagnostic information on current pulmonary, critical care, and sleep medicine issues.

Earn up to 24 *AMA PRA Category 1 credit(s)*. One (1) credit will be awarded for each completed lesson.

Lessons for May 2008:

- **Obesity and Pulmonary Dysfunction**

By Akshay Sood, MD, MPH; and Kathia Ortiz-Cantillo, MD

- **Complex Sleep Apnea**

By Akram Khan, MD; and Peter C. Gay, MD, FCCP

'One Wiz With': Cheesesteaks and CHEST 2008

CHEST 2008
Philadelphia
October 25 - 30, 2008

Rich in American history, Philadelphia is largely recognized as the birthplace of life, liberty, the pursuit of happiness … and cheesesteak. Cheesesteaks made their debut in South Philadelphia in 1930. Today, a trip to Philly isn't complete unless you've had at least one of these famed sandwiches. Here are a few tips to help you enjoy a cheesesteak during CHEST 2008.

First, you should know how to order. The idea is to let the cook know (a) you want a cheesesteak, (b) the type of cheese you want—Cheez Whiz®, American, or provolone, and (c) whether or not you want fried onions. Be as concise as possible. Locals have it down to three words. Ordering "one wiz with" means you'd like one cheesesteak (denoted by "one") with Cheez Whiz® (denoted by "wiz"), and with fried onions (denoted by "with"). Similarly, saying, "one provolone without," will secure you a cheesesteak with provolone cheese and no fried onions. Got it?

The art of cheesesteak preparation lies in the balance of flavors, textures, and what is often referred to as the "drip" factor. You'll know you have a good cheesesteak if juices are dripping from the bun. In order to avoid ruining their clothes, Philadelphians have learned the "Philadelphia Lean." It's advised that you do the same. Follow their example by bending forward to eat your cheesesteak instead of bringing it to your mouth.

As you might imagine, there's much more to Philadelphia and CHEST 2008 than cheesesteak. Learn more about Philly's cultural, culinary, and recreational options at www.gophila.com, and watch for details about CHEST 2008, October 25-30, at www.chestnet.org. ■

CLASSIFIEDS

Also available at www.elsevierhealthcareers.com

PROFESSIONAL OPPORTUNITIES

Marietta Pulmonary Medicine Suburban Atlanta

Well-established, busy eleven-physician single-specialty Pulmonary practice in suburban Atlanta, Georgia, looking for one or more BC/BE Pulmonary/Critical Care physicians. Sleep certification is a plus. Practice includes all aspects of pulmonary medicine, including critical care, sleep medicine, out-patient clinic, pulmonary rehab and clinical research. Practice located at two large acute-care hospitals, with one being the busiest ER in Georgia, and also rounds at a near-by long term acute care hospital. Competitive salary with bonus potential and generous benefits package. Fax CV to: 770-792-1738.

Pulmonologist

Mercy Hospital of Tiffin, located in Tiffin, Ohio, was founded more than 93 years ago on a compassionate mission of serving our patients needs. Weíve seen their need and medical technology, change dramatically through the decades. It's why we're investing nearly $60 million in our facilities and service through the Designing Our Future Project. A major part of the Designing Our Future Project is the construction of a 140,000 square foot hospital and the recruitment of a pulmonologist. The hospital will feature 67 private rooms and the most advanced technology designed to enhance the delivery of patient care. The new hospital will make it easy for patients to access the site and navigate through the facility. Plans also include enhanced outpatient service capabilities and surgery suites designed and equipped with the latest technology. If you are considering career opportunities in a safe community with wonderful schools, and an enviable quality of life and the absence of large city medical staff politics, we would like to speak with you in confidence. Inquiries, including curriculum vitae should be addressed to: Tom Leeds, Medical Staff Recruiter, Mercy Health Partners, 2200 Jefferson Avenue, Toledo, Ohio 43604 or call 1-800-837-4664, extension 3999.

SOUTHERN CALIFORNIA PULMONARY/CRITICAL CARE OPPORTUNITY

Looking for BC/BE Pulmonologist/CCM Physician to join large, successful pulmonary practices in the area. Great location. Offers excellent benefits, early partnership, and great growth potential. Fax CV to: 626-795-2716 Attn: Tania or email to taniakure@yahoo.com

BEAUTIFUL COAST OF MAINE BC/BE Pulmonologist

Multi-specialty, community hospital seeks full-time physician for outpatient practice. Belfast is safe and offers beautiful views of Penobscot Bay. Ideal for outdoor enthusiasts. Family oriented with excellent schools. Immediate availability.
Contact Mark Biscone, Executive Director Waldo County General Hospital, PO Box 287, Belfast, ME 04915, 207-338-9302
E-mail: ceo@wchi.com
Website: www.wchi.com

Pulmonary Critical Care Opportunity
Northern California

Sutter Medical Group (SMG) is seeking a BE/BC Pulmonary Critical Care physician in Auburn, CA. Good call schedule. Option for hospitalist work if desired.

SMG is a multi-specialty group of over 300+ members. SMG offers an income guarantee with shareholder track, generous compensation, benefits, and retirement package.

Sutter Auburn Faith Hospital is a medium sized hospital with a 24/7 hospitalist program, open ICU, high resolution CT scan, cardiac cath lab, full nuclear medicine department, bronchoscopy suites and a pulmonary function laboratory.

Auburn is centrally located in the Sierra Nevada foothills between Sacramento and Lake Tahoe. Auburn is close to shopping and restaurants, and offers a variety of outdoor activities.

Physician Recruitment
800-650-0625
916-643-6677 fax
develops@sutterhealth.org
www.sutterhealth.org

Sutter Health
Sacramento Sierra Region
With You. For Life.

FOR INFORMATION ON CLASSIFIEDS:

Contact: Rhonda Beamer, Walchli Tauber Group, Inc., 2225 Old Emmorton Road, Suite 201, Bel Air, MD 21015. (443) 512-8899 Ext 106. FAX: (443) 512-8909.
Email ad to: rhonda.beamer@wt-group.com

Disclaimer

CHEST PHYSICIAN assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.

DORIBAX™
(doripenem for injection)
for Intravenous Infusion

Brief Summary: The following is a brief summary only. Before prescribing, see complete Prescribing Information in DORIBAX™ (doripenem for injection) labeling.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
DORIBAX™ is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS:
Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with DORIBAX™ is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross-hyperreactivity among beta-lactam antibiotics has been clearly documented.

If an allergic reaction to DORIBAX™ occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Interaction with Sodium Valproate: Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur. *[see Drug Interactions]*

***Clostridium difficile*-Associated Diarrhea:** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated. *[see Adverse Reactions]*

Development of Drug-Resistant Bacteria: Prescribing DORIBAX™ in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Pneumonitis with Inhalational Use: When DORIBAX™ has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX™ should not be administered by this route.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of labeling:

- Anaphylaxis and serious hypersensitivity reactions *[see Warnings and Precautions]*
- Interaction with sodium valproate *[see Warnings and Precautions* and *Drug Interactions]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions]*
- Development of drug-resistant bacteria *[see Warnings and Precautions]*
- Pneumonitis with inhalational use *[see Warnings and Precautions]*

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

During clinical investigations, 853 adult patients were treated with DORIBAX™ IV (500 mg administered over 1 hour q8h) in the three comparative phase 3 clinical studies; in some patients, parenteral therapy was followed by a switch to an oral antimicrobial. *[see Clinical Studies (14)* in full Prescribing Information*]* The median age of patients treated with DORIBAX™ was 54 years (range 18-90) in the comparative cUTI study and 46 years (range 18-94) in the pooled comparative cIAI studies. There was a female predominance (62%) in the comparative cUTI study and a male predominance (63%) in the pooled cIAI studies. The patients treated with DORIBAX™ were predominantly Caucasian (77%) in the three pooled phase 3 studies.

The most common adverse reactions (≥ 5%) observed in the DORIBAX™ phase 3 clinical trials were headache, nausea, diarrhea, rash and phlebitis. During clinical trials, adverse drug reactions that led to DORIBAX™ discontinuation were nausea (0.2%), vulvomycotic infection (0.1%) and rash (0.1%).

Adverse reactions due to DORIBAX™ 500 mg q8h that occurred at a rate ≥1 % in either indication are listed in Table 1. Hypersensitivity reactions related to intravenous study drug and *C. difficile* colitis occurred at a rate of less than 1% in the three controlled phase 3 clinical trials.

Table 1: Adverse Reactions† with Incidence Rates (%) of ≥1% and Adverse Events†† Having Clinically Important Differences in Frequency by Indication in the Three Controlled, Comparative DORIBAX™ Phase 3 Clinical Trials

	Complicated Urinary Tract Infections (one trial)		Complicated Intra-Abdominal Infections (two trials)	
System organ class	DORIBAX™ 500 mg q8h (n =376)	Levofloxacin 250 mg IV q24h (n = 372)	DORIBAX™ 500 mg q8h (n = 477)	Meropenem 1 g q8h (n = 469)
Nervous system disorders				
Headache	16	15	4	5
Vascular disorders				
Phlebitis	4	4	8	6
Gastro-intestinal disorders				
Nausea	4	6	12	9
Diarrhea	6	10	11	11
Blood and Lymphatic System Disorders				
Anemia††	2	1	10	5
Renal and Urinary Disorders				
Renal impairment/ Renal failure††	<1	0	1	<1

Table 1: Adverse Reactions† with Incidence Rates (%) of ≥1% and Adverse Events†† Having Clinically Important Differences in Frequency by Indication in the Three Controlled, Comparative DORIBAX™ Phase 3 Clinical Trials *(continued)*

	Complicated Urinary Tract Infections (one trial)		Complicated Intra-Abdominal Infections (two trials)	
System organ class	DORIBAX™ 500 mg q8h (n =376)	Levofloxacin 250 mg IV q24h (n = 372)	DORIBAX™ 500 mg q8h (n = 477)	Meropenem 1 g q8h (n = 469)
Skin and subcutaneous disorders				
Pruritus	<1	1	3	2
Rash*	1	1	5	2
Investigations				
Hepatic enzyme elevation**	2	3	1	3
Infection and Infestations				
Oral candidiasis	1	0	1	2
Vulvomycotic infection	2	1	1	<1

* includes reactions reported as allergic and bullous dermatitis, erythema, macular/papular eruptions, urticaria and erythema multiforme
** includes reactions reported as alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased
† An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.
†† An adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Postmarketing Experience: The following adverse reaction has been identified during post-approval use of doripenem outside of the U.S. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency or establish a causal relationship to drug exposure.

Anaphylaxis

The following treatment-emergent adverse events (known to occur with beta-lactams including carbapenems) have been reported voluntarily during post-approval use of DORIBAX™ outside of the U.S. They are included due to their seriousness, although it is not possible to estimate their frequency and causality has not been established:

Stevens Johnson Syndrome
Toxic epidermal necrolysis
Interstitial pneumonia
Seizure

DRUG INTERACTIONS
Valproic Acid: A clinically significant reduction in serum valproic acid concentrations has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or a seizure occurs. *[see Warnings and Precautions]*

Probenecid: Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. *[see Clinical Pharmacology (12.3)* in full Prescribing Information*]* Coadministration of probenecid with DORIBAX™ is not recommended.

USE IN SPECIFIC POPULATIONS
Pregnancy: Category B: Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least 2.4 and 0.8 times the exposure to humans dosed at 500 mg q8h, respectively). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX™ is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of subjects in clinical studies of DORIBAX™, 28% were 65 and over, while 12% were 75 and over. Clinical cure rates in complicated intra-abdominal and complicated urinary tract infections were slightly lower in patients ≥65 years of age and also in the subgroup of patients ≥75 years of age versus patients <65. These results were similar between doripenem and comparator treatment groups.

No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Elderly subjects had greater doripenem exposure relative to non-elderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. *[see Clinical Pharmacology (12.3)* in full Prescribing Information*]*

This drug is known to be excreted substantially by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function or pre-renal azotemia. Because elderly patients are more likely to have decreased renal function or pre-renal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function.

Patients with Renal Impairment: Dosage adjustment is required in patients with moderately or severely impaired renal function. *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in full Prescribing Information*]* In such patients, renal function should be monitored.

PATIENT COUNSELING INFORMATION

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report any previous hypersensitivity reactions to DORIBAX™, other carbapenems, beta-lactams or other allergens.
- Patients should be counseled that anti-bacterial drugs including DORIBAX™ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORIBAX™ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORIBAX™ or other antibacterial drugs in the future.
- Keep out of the reach of children.

MINI-BAG Plus is a trademark of Baxter International Inc.

Manufactured by:
Shionogi & Co. Ltd.
Osaka 541-0045, Japan

Distributed by:
Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869

10157600B 10/2007

- Clinical efficacy proven in complicated intra-abdominal infections* and complicated urinary tract infections, including pyelonephritis†
- Demonstrated safety and tolerability profiles—no seizures reported in 4 large Phase III clinical trials

Carbapenem potency that breaks through today's gram-negative pathogens‡[1-3]

- Proven in vitro activity vs *P aeruginosa*, Enterobacteriaceae, and *A baumannii*[1-3]

‡ In vitro activity does not necessarily correlate with clinical results.

Please see brief summary of full Prescribing Information on following pages.

DORIBAX™
doripenem for injection

TOUGH TO RESIST

* DORIBAX is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by susceptible strains of *E coli*, *K pneumoniae*, *P aeruginosa*, *B caccae*, *B fragilis*, *B thetaiotaomicron*, *B uniformis*, *B vulgatus*, *S intermedius*, *S constellatus*, or *P micros*.

† DORIBAX is indicated as a single agent for the treatment of complicated urinary tract infections caused by susceptible strains of *E coli*, including cases with concurrent bacteremia, *K pneumoniae*, *P mirabilis*, *P aeruginosa*, or *A baumannii*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX and other antibacterial drugs, DORIBAX should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Important Safety Information

DORIBAX is contraindicated in patients with known serious hypersensitivity to doripenem or other carbapenems, or in patients who have demonstrated anaphylactic reactions to beta lactams.

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. If an allergic reaction to DORIBAX occurs, discontinue the drug.

Serious acute anaphylactic reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur.

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued.

When doripenem has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX should not be administered by this route.

Safety and effectiveness in pediatric patients have not been established.

The most common adverse reactions (≥5%) observed in clinical trials were headache, nausea, diarrhea, rash, and phlebitis.

REFERENCES: 1. Evangelista AT, Yee C, Pillar CM, Aranza-Torres MK, Sahm DF, Thornsberry C. Surveillance profiling of doripenem activity against *Pseudomonas aeruginosa* isolated from inpatients and ICU patients: results of the TRUST surveillance initiative. Presented at the 45th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2007: San Diego, CA. **2.** Data on file. Ortho-McNeil-Janssen Pharmaceuticals, Inc. **3.** Jones ME, Draghi DC, Brown NP, Aranza MK, Thornsberry C, Sahm DF, et al. Baseline surveillance profile of Doripenem (DOR) against key gram-negative pathogens encountered in the United States. Presented at the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2006:San Francisco, CA.

For more information, visit us at www.doribax.com

ORTHO-McNEIL™
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

SHIONOGI & CO., LTD.

May 2008 02B07140TR2